Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Alzheimer's Agents
Cholinesterase Inhibitors, AHFS Class 120400 and
NMDA Receptor Antagonists, AHFS Class 289200
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I. Overview

Alzheimer's disease (AD) is a progressive disease that affects both cognition and behavior. AD is classified under Delirium, Dementia, and Amnestic and Other Disorders in the *Diagnostic and Statistical Manual for Mental Disorders*, 4th edition (DSM-IV-TR). It is defined as the development of multiple cognitive deficits manifested by memory impairment and one or more of the following: aphasia, apraxia, agnosia, and disturbance in executive functioning. Pathophysiologic mechanisms behind the disease are not entirely understood, but a common pathologic finding is the accumulation of beta-amyloid proteins in the brain. Subsequently, inflammatory and free radical processes eventually result in neuron dysfunction and death. Although research is looking at preventing plaque formation or enhancing plaque removal, current drug therapies target symptom reduction and a slowing of the signs of cognitive decline.

The course of the disease starts with mild cognitive impairment, progresses to more severe effects and, eventually, death, commonly due to pneumonia or aspiration. Predictors of mortality include severity at time of diagnosis, abnormal neurologic findings, and the presence of heart disease and diabetes.[1] AD is the most common of the dementias in the US accounting for more than 50% of all diagnosed dementias. Based on 2000 data, more than 4.5 million people in the United States have AD. 93% of all cases occur in people older than 74 years of age.[2]

By 2050, one in five people will be over age 65 years, and the number of Alzheimer's patients is projected to be 11.3-16 million.[2] Although there is no definitive diagnostic laboratory, clinical, or imaging tests available, neuropsychological testing and clinical evaluation is 90% accurate. Treatment consists of nonpharmacologic and pharmacologic therapies, with nonpharmacologic interventions as the primary mechanism for management of memory loss and behavioral symptoms of AD. Nonpharmacologic therapies consist of keeping a notepad in one's pocket to make reminders, posting lists and notes throughout the house, exercising one's brain through reading and crossword puzzles, and other strategies. Medications are used in the context of multimodal interventions, and in 2002, accounted for 8.2 prescriptions per 1000 members of a healthcare program.[3] Current pharmacotherapy is aimed at reducing the rate of cognitive decline. Behavioral conditions also show some improvement with this class of medications but, once again, treatment is geared towards reducing symptoms instead of curing or arresting the disease.

There are four cholinesterase inhibitor medications and one N-methyl-D-aspartate (NMDA) receptor antagonist being reviewed. At this time, there are no generic alternatives to any of the Alzheimer's medications. This review encompasses all dosage forms and strengths.

Table 1. Alzheimer's Agents Included in this Review

Drug Classification	Generic Name*	Formulation	Example Brand Name(s)
Cholinesterase Inhibitor	Donepezil	Oral	Aricept®, Aricept ODT®
	Tacrine	Oral	Cognex®
	Rivastigmine	Oral	Exelon®
	Galantamine	Oral	Razadyne® (formerly Reminyl®), Razadyne ER®
NMDA Receptor Antagonist	Memantine	Oral	Namenda®

* There are no generic or over-the-counter formulations available for any of the medications in this class.

II. Evidence Based Medicine and Current Treatment Guidelines

Until recently, the cholinesterase inhibitors were the only drugs indicated for first-line treatment of cognitive symptoms in AD. It is believed that the memory loss in Alzheimer's disease is the result of a deficiency of cholinergic neurotransmission. Increasing cholinergic function is the primary mechanism of action of the cholinesterase inhibitors. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, does not directly increase acetylcholine effects but seems to preserve neuronal function. Memantine is FDA indicated only for moderate to severe dementia and the cholinesterase inhibitors are indicated for mild to moderate disease.

Head-to-head trials comparing the efficacy of the cholinesterase inhibitors are limited. The Alzheimer's Association, The American Association for Geriatric Psychiatry, The American Geriatrics Society and other organizations have published treatment guidelines for the disease in hopes that early and accurate diagnosis and treatment of related disorders will benefit patients and caregivers. However, these guidelines are slightly dated and do not reflect more recently published information regarding head to head results, long term safety and efficacy data, combination therapy and the recently determined risk of all cause mortality when using Vitamin E at greater then 400IU a day.

Table 2. Treatment Guidelines Using the Alzheimer's Agents

Diagnosis and treatment of Alzheimer's disease and related disorders: Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society[4]
Diagnosis Definition of dementia: The DSM-IV is a reliable definition and should be routinely used. Criteria for establishing the diagnosis of prevalent dementing illnesses: The NINCDS-ADRDA criteria for the diagnosis of probable AD or DSM-IIIR criteria should be routinely used. Clinical criteria for Creutzfeldt-Jakob disease should be used in rapidly progressive dementia syndromes. Practice Options: • The Hachinski Ischemic Index may be of use in the diagnosis of cerebral vascular disease in dementia. • The consortium for dementia with Lewy-bodies diagnostic criteria may be of use in clinical practice. • The consensus diagnostic criteria for frontotemporal dementia may be of use in clinical practice. Structural neuroimaging for the differential diagnosis of dementing illness: • Structural neuroimaging with either a noncontrast CT or MR scan in the routine initial evaluation of patients with dementia is appropriate. • Linear or columetric MR or CT measurement strategies for the diagnosis of AD are not recommended. Genetic biomarkers for counseling patients with dementia or their families: • Genetic testing for suspected AD is not recommended. • Testing for tau mutation or AD gene mutations is not recommended for routine evaluation. **Management of Dementia: Pharmacologic treatment of dementia and non-cognitive behaviors of dementia, non-pharmacologic management of symptoms, and educational initiatives for families of patients with dementia** Pharmacologic treatment of Alzheimer's disease: • Cholinesterase inhibitors should be considered in patients with mild to moderate AD, although studies suggest a small average degree of benefit. • Vitamin E (1000 I.U. PO BID) should be considered in an attempt to slow progression of AD. • There is insufficient evidence to support the use of other antioxidants, anti-inflammatories, or other putative disease-modifying agents specifically to treat AD because of the risk of significant side effects in the absence of demonstrated benefits. • Estrogen should not be prescribed to treat AD. • Some patients with unspecified dementias may benefit from ginkgo biloba, but evidence-based efficacy data are lacking. Pharmacologic treatment for noncognitive symptoms of dementia: • Antipsychotics should be used to treat agitation or psychosis in patients with dementia where environmental manipulation fails. Atypical agents (risperidone, olanzapine, and quetiapine) may be better tolerated compared with traditional agents (haloperidol). • Selected antidepressants (e.g. tricyclics and SSRIs) should be considered in the treatment of depression in individuals with dementia with side effect profiles guiding the choice of agent. Educational interventions for patients with dementia and/or caregivers: • Short-term programs directed toward educating family caregivers about AD should be offered to improve caregiver satisfaction. • Intensive long-term education and support services should be offered to caregivers of patients with AD to delay time to nursing home placement. • Staff of long-term care facilities should receive education about AD to reduce the use of unnecessary antipsychotics. As part of this practice guideline, additional interventions other than education for patients and caregivers, are available for functional behaviors, problem behaviors, and care environment alterations.

NINCDS = National Institute of Neurological and Communicative Disorders and Stroke
ADRDA = Alzheimer's Disease and Related Disorders Association

III. Indications

In the early 1980s, tacrine was the first drug evaluated as a means to enhance cholinergic activity in patients with AD. Due to an extensive adverse effect profile, use of tacrine has been replaced by more

tolerable cholinesterase inhibitors. Also, due to a risk of hepatotoxicity, tacrine is contraindicated in patients with liver disease. Donepezil has specificity for inhibition of acetylcholinesterase compared to butyrylcholinesterase, which results in fewer side effects (e.g. nausea, vomiting, and diarrhea) but may make it less effective in late stages of Alzheimer's disease since butyrylcholinesterase is more abundant than acetylcholinesterase in patients with late stages of the disease. Rivastigmine has central activity for acetylcholinesterase and butyrylcholinesterase, with low affinity at these sites in the periphery. The most recently approved cholinesterase inhibitor, galantamine, is specific for acetylcholinesterase and has activity as a nicotinic receptor modulator which results in acetylcholine binding more tightly to the receptor.

Cholinesterase inhibitors should be used with caution in patients with asthma, chronic obstructive pulmonary disease, sick sinus syndrome, or other supraventricular cardiac conditions. In addition, due to the mechanism of action of the cholinesterase inhibitors, gastric acid secretion may be increased as a result of increased cholinergic activity. Therefore, special caution should be used in patients at increased risk of developing ulcers or those with a history of peptic ulcer disease.

Memantine effects the transmission of glutamate by weakly and uncompetively blocking cation channels on the glutamate neuron. This weak binding does not allow for chronic stimulation which may damage neurons but does allow for bursts of excitation which allows for appropriate signal transmission.[6] Abnormal glutamatergic activity, in addition to causing cognitive deficits, may cause neuronal toxicity thought to be involved in the destruction of brain cells in AD patients. The drug appears to inhibit abnormal glutamatergic activity and slow the cognitive, functional, and global deterioration apparent in patients with moderate to severe AD.

Table 3 summarizes the FDA-approved indications for these drugs.

Table 3. FDA-Approved Indications for the Alzheimer's Agents[5, 6]

Agent	Mild-Moderate Dementia of the Alzheimer's Type	Moderate-Severe Dementia of the Alzheimer's Type
Donepezil	□	
Tacrine	□	
Rivastigmine	□	
Galantamine	□	
Memantine		□

IV. Pharmacokinetics

The pharmacokinetic parameters for each of the agents in this class vary in some respects. Galantamine and donepezil are metabolized primarily by cytochrome P450 (CYP450) 2D6 and 3A4. Tacrine is metabolized by cytochrome P450 also but uses the isoenzyme 1A2 and not 2D6. Rivastigmine is metabolized by plasma esterases and not the CYP450 group of isoenzymes. Memantine is generally eliminated unchanged through the kidneys.

Protein binding rates and absolute bioavailabilities vary among these medications.

Galantamine ER is galantamine HCl encased in a slow release capsule. The pharmacokinetics of the two delivery methods are equal except for the time to maximum concentration, which occurs later, and peak levels, which are lower with the ER version.

Table 4 compares additional pharmacokinetic parameters for the drugs used to treat AD.

Table 4. Pharmacokinetic Parameters of the Alzheimer's Agents [5, 6, 7, 8]

Agent	t_{max} (hr)	Absolute Bioavail-ability	Food Effect	Protein Binding	Metabolism	Elimination
Donepezil	3-4	100%	None	96%	Cytochrome P450 2D6 and 3A4, and glucuronidation	Half-life is 70 hours; 57% renal
Tacrine	1-2	17%	Reduced bioavailability 30-40%*	55%	Cytochrome P450 1A2	First-pass effect, half-life is 2-4 hours
Rivastigmine	1	36%	T_{max} is delayed by 90 min; ↓ C_{max} by 30%; AUC ↑ by 30%	40%	Cholinesterase-mediated hydrolysis; minimal CYP450 involvement	Half-life is 1.4-1.7 hours; 97% renal
Galantamine	1	90%	AUC is unaffected; C_{max} ↓ by 25% and T_{max} delayed by 1.5 hours	18%	Cytochrome P450 2D6 and 3A4	Half-life is 7 hours; primarily renal
Memantine	3-7	100%	None	45%	80% excreted unchanged in the urine; hepatic, non-CYP450 metabolism	Half-life is 60-80 hours; predominately renal (57%-82%)

*Food has no effect if tacrine is administered at least 1 hour before meals.

V. Drug Interactions

Cholinesterase Inhibitors
All of the cholinesterase inhibitor drugs used to treat AD will have a decreased effect when administered with anticholinergic medications such as oxybutynin, diphenhydramine, benztropine, tricyclic antidepressants, and conventional antipsychotics. More detailed information specific to each agent is presented below, followed by documented drug-interactions in Table 5. Since rivastigmine is not metabolized by cytochrome P450, it will have fewer pharmacokinetic drug interactions.

Donepezil
Due to high protein binding with donepezil, displacement studies with other highly bound drugs such as warfarin, furosemide, and digoxin have been performed. Donepezil at concentrations of 0.3-10mcg/ml did not affect the binding of furosemide, digoxin, or warfarin to human albumin, and similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin. *In vitro* studies with donepezil show a slow rate of binding to the cytochrome P450 3A4 and 2D6 enzymes, indicating little likelihood of inhibition by donepezil. It is not known whether donepezil has potential for enzyme induction.

It is likely that inhibitors and inducers of CYP2D6 and 3A4 (e.g. fluoxetine, phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could alter the rate of elimination of donepezil.

Tacrine
Drug interactions with tacrine may occur with agents that undergo extensive metabolism via cytochrome P450 1A2. Many of these interactions are detailed in Table 5.

Rivastigmine
Because rivastigmine is metabolized by esterases rather than CYP enzymes, no drug interactions with drugs metabolized by the following isoenzymes are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.[11] No interactions have been observed in studies between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine. In addition, drugs that inhibit or induce CYP450 are not expected to alter the metabolism of rivastigmine.

Galantamine
Galantamine does not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6, or CYP2E1. Potential changes in serum levels of galantamine exist when coadministered with fluoxetine, cimetidine, ketoconazole, erythromycin, paroxetine and other medications that inhibit or induce CYP450 2D6 and 3A4.

NMDA-Receptor Antagonist

Memantine
In vitro studies suggest memantine exhibits minimal inhibition of CYP450. The potential for drug interactions is very low as the drug is excreted in a mainly unmetabolized form, with low serum protein binding. In vitro investigations of the potential for interactions with memantine and donepezil, galantamine, and tacrine have demonstrated that memantine does not effect the pharmacodynamics of acetylcholinesterase by these drugs.[9, 10]

In vivo studies of memantine and donepezil in 24 patients, showed no clinically significant differences in the kinetics of memantine or donepezil, or in the inhibition of acetylcholinesterase by donepezil when the drugs were administered alone or in combination.[10] Because memantine is eliminated by renal tubular secretion, the interaction between memantine and triamterene / HCTZ was investigated in 20 subjects. Triamterene / HCTZ did not alter the bioavailability of memantine at steady state. Memantine did not affect the bioavailability of triamterene and its metabolite, but did cause a reduction of about 20% in the bioavailability of HCTZ.

When administered under alkaline urine conditions, the clearance of memantine was reduced by about 80% at a urine pH of 8. Drugs that increase the pH of the urine, such as sodium bicarbonate and carbonic anhydrase inhibitors, would be expected to reduce the elimination of memantine.

In double-blind, placebo-controlled trials with memantine, 89% of patients in both treatment groups used concomitant medications during the trial.[9] No clinically meaningful differences were observed in the frequency of adverse events in patients taking memantine and concomitant medications compared with those patients not taking concomitant medications.

Table 5. Significant Drug Interactions with the Alzheimer's Agents[12]

Significance	Interaction	Mechanism
2 Delayed, Moderate, Suspected	Tacrine and fluvoxamine	Possible inhibition of tacrine metabolism (CYP1A2) by fluvoxamine resulting in elevated tacrine concentrations and increased pharmacologic and adverse effects of tacrine.
4 Delayed, Moderate, Possible	Tacrine and cimetidine	Inhibition of first-pass hepatic metabolism of tacrine may lead to elevated tacrine concentrations, increasing the pharmacologic and adverse effects. In one study, cimetidine increased the C_{max} and AUC of tacrine by 54% and 64%, respectively.
4 Delayed, Moderate, Possible	Tacrine and ibuprofen	Mechanism is unknown. Delirium was reported during concurrent administration of ibuprofen and tacrine.

Significance	Interaction	Mechanism
4 Delayed, Moderate, Possible	Tacrine and levodopa	Possible worsening of cholinergic activity in patients with parkinsonism due to central cholinesterase inhibitor activity of tacrine, causing levodopa in patients with parkinsonism to be inhibited.
4 Delayed, Moderate, Possible	Tacrine and theophylline/aminophylline	Possible inhibition of the hepatic metabolism of theophylline, resulting in increased theophylline concentrations and toxicity.
5 Rapid, Minor, Possible	Donepezil and antifungals (fluconazole, itraconazole, ketoconazole, and miconazole)	Azole antifungal agents may inhibit the metabolism (CYP3A4) of donepezil causing the plasma concentration of donepezil to be increased.

VI. Adverse Drug Events

Historically, about 17% of patients who receive tacrine withdraw from treatment permanently due to adverse events.[8] Transaminase elevations were the most common reason for withdrawals, accounting for 8% of all tacrine-treated patients. Transaminase elevations occur infrequently with the other Alzheimer's agents. For this reason, tacrine use is disadvantageous compared to the other agents in this class. Discontinuations due to adverse events for rivastigmine, donepezil, and galantamine are low and similar to placebo. Gastrointestinal (GI) adverse events occur most frequently among the cholinesterase inhibitor agents. Donepezil frequently results in lower GI adverse events compared to the other agents. Table 6 illustrates the common adverse events reported for the cholinesterase inhibitors.

Table 6. Common Adverse Events (%) Reported for the Cholinesterase Inhibitors[5,6]

Adverse Event	Donepezil	Tacrine	Rivastigmine	Galantamine
Elevated liver function tests	NR	29%	NR	NR
Nausea and vomiting listed together		28%		
Nausea	11%		47%	24%
Vomiting	5%		31%	13%
Diarrhea	10%	16%	19%	9%
Headache	10%	11%	17%	8%
Dizziness	8%	12%	21%	9%
Muscle cramps	6%	9%	NR	NR
Insomnia	9%	6%	9%	5%
Fatigue	5%	4%	9%	5%
Anorexia	4%	9%	17%	9%
Depression	3%	4%	6%	7%
Abnormal dreams	3%	NR	NR	NR
Weight increase	3%	3%	3%	7%
Somnolence	2%	4%	5%	4%
Abdominal pain	NR	8%	13%	5%
Tremor	NR	2%	4%	3%
Agitation	NR	7%	NR	NR
Rhinitis	NR	8%	NR	NR

NR = Incidence not reported

Memantine

In double-blind, placebo-controlled dementia trials (940 memantine-treated patients, 922 placebo-treated patients) 1,286 patients reported treatment-emergent adverse events. A comparable number of placebo-treated patients (624) and memantine-treated patients (662) reported a treatment-emergent adverse event.[6] Most treatment-emergent adverse events were considered mild or moderate in severity and not related to the trial drug.

Dizziness, confusion, headache, and constipation were reported in greater than 5% of memantine patients and at an incidence greater than placebo, while agitation, fall, and accidental injury occurred in greater than 5% of placebo patients at an incidence greater than memantine.[6] Treatment-emergent adverse events occurring in ≥ 5% of either placebo or memantine treated patients are shown in Table 7. The number of treatment-emergent adverse events did not vary by dementia diagnosis or severity and events were similar between treatment groups. The incidence of serious adverse events did not vary between placebo-treated patients and memantine-treated patients (14.6% vs. 13.5%, respectively).

Table 7. Treatment-Emergent Adverse Events in ≥ 5% of Patients[6, 8]

Adverse Event	Placebo (n=922) n (%)	Memantine (n=940) n (%)
Dizziness	49 (5.3)	64 (6.8)
Agitation	98 (10.6)	63 (6.7)
Confusion	42 (4.6)	58 (6.2)
Headache	31 (3.4)	54 (5.7)
Constipation	28 (3.0)	50 (5.3)
Fall	50 (5.4)	48(5.1)
Accidental Injury	64 (6.9)	44 (4.7)

Adverse events were the most common reason for discontinuation of memantine in pre-marketing trials (11.5% placebo vs. 10.1% memantine). In one double-blind, placebo-controlled trial, memantine was administered in combination with donepezil; the addition of memantine resulted in substantially fewer discontinuations due to any adverse event (7.4%) compared to donepezil and placebo treatment.[13] In four open-label extension studies, discontinuation due to any adverse event was similar between treatment groups (9.8% placebo-memantine, 11.6% memantine-memantine).

VII. Dosing and Administration

Donepezil and galantamine ER are the only agents approved for once daily dosing. Rivastigmine, galantamine and memantine are available in a liquid dosage form and donepezil is available as an orally disintegrating tablet (ODT). Although studies indicate the clearance of donepezil and rivastigmine may be altered in renal and hepatic impairment, neither manufacturer has provided specific recommendations for dosing in patients with renal or hepatic disease. Galantamine use is not recommended in patients with severe hepatic or renal impairment, and caution should be used when the drug is given to patients with moderate hepatic or renal disease. Tacrine should be used with caution in patients with pre-existing liver disease, and in renal impairment, especially in the event of electrolyte disturbances from adverse GI events. When given with food, the GI tolerability of the cholinesterase inhibitors may be improved.

Table 8 further describes the dosing regimens for the agents in this review.

Table 8. Dosing for the Alzheimer's Drugs[2, 5, 6, 7, 8]

Agent	Availability	Dose /Frequency/Duration
Donepezil	5mg and 10mg tablets and orally disintegrating tablets (ODT)	Starting: 5mg QHS, with or without food Maintenance: 5-10mg QD Time between dosage adjustment: 4-6 weeks
Tacrine	10mg, 20mg, 30mg, and 40mg capsules	Starting: 10mg QID at least 1 hour before meals Maintenance: 20-40mg QID Time between dosage adjustment: 4-6 weeks
Rivastigmine	1.5mg, 3mg, 4.5mg, 6mg capsules and oral solution 2mg/ml	Starting: 1.5mg BID with the morning and evening meals Maintenance: 3-6mg BID Time between dosage adjustment: 2 weeks

Agent	Availability	Dose /Frequency/Duration
Galantamine	4mg, 8mg, and 12mg tablets and oral solution 4mg/ml, ER tablet 8mg, 16mg, and 24mg	Starting: 4mg BID with the morning and evening meals, ER tablet: 8mg QD Maintenance: 8-16mg BID, ER: 16-24mg QD Time between dosage adjustment: 4 weeks
Memantine	5mg and 10mg tablets and oral solution 2mg/ml, 4 week titration pak	Week 1: 5mg QD Week 2: 10mg/day (5mg BID) Week 3: 15mg/day (10mg QAM, 5mg QPM) Week 4: maintenance dose, 20mg/day (10mg BID)

Special Dosing Considerations

Renal and Hepatic Insufficiency:

- There are no specific manufacturers' recommendations for dosing adjustments with donepezil in patients who have renal or hepatic insufficiency.
- The use of galantamine should be restricted in patients with hepatic or renal insufficiency: it is not recommended in patients with severe hepatic or renal impairment and caution is recommended for patients with moderate hepatic or renal disease.
- Dosing adjustments with rivastigmine are not necessary in hepatic disease or renal disease as the drug is individually titrated to tolerability.
- Tacrine should be used with extreme caution in patients with hepatic and renal impairment.
- Memantine: in patients with moderate renal impairment, dosage reduction should be considered with memantine. Use of memantine in severe renal impairment has not been evaluated and is not recommended. The kinetics of memantine in patients with hepatic impairment have not been investigated, but would be expected to be only modestly affected.[6, 7]

VIII. Effectiveness

Until recently, there were no head-to-head trials comparing the efficacy of the cholinesterase inhibitors in Alzheimer's disease. Limited comparative data is now available. As memantine is the only NMDA receptor antagonist, comparative data is not available. However, memantine has been studied in combination with donepezil. Memantine has been studied in Europe during the last decade for the treatment of dementia, and was approved in the European Union in May of 2002 for the treatment of moderately severe to severe AD. In 2003, the FDA gave memantine approval for the treatment of moderate to severe AD but not for mild AD.

A number of studies have evaluated the effect of switching from donepezil to rivastigmine. Studies indicate that approximately 50% of patients who experience lack or loss of efficacy with donepezil respond to treatment with rivastigmine.[14] The same studies also indicate that safety and tolerability problems with donepezil are not predictive of similar problems with rivastigmine. Another study looked at switching donepezil to galantamine with either a 4 day washout period or a 7 day washout period.[15] The authors found that there was no difference in tolerability between the two methods of conversion. One study[16] reviewed 3 comparative studies, donepezil vs. rivastigmine,[17] galantamine vs. donepezil,[18] and donepezil vs. galantamine,[19] and assessed them for quality. The authors concluded that these 3 studies were methodologically flawed to the point where the validity in the outcomes is questionable.

Kaduszkiewicz et al.[20] conducted a systematic review of all randomized-controlled trials of donepezil, rivastigmine and galantamine published in 1989-2004. They found 22 trials which met the inclusion criteria: 12 for donezepil, 5 for rivastigmine and 5 for galantamine. The authors found that the differences in efficacy among the 3 medications vary by study and that the overall efficacy versus placebo is moderate. They concluded that "the scientific basis for recommendations of the cholinesterase inhibitors for Alzheimer's Disease is questionable."

Table 9 illustrates important efficacy trials for the Alzheimer's drugs.

Table 9. Outcomes Evidence for the Alzheimer's Agents

Study	Sample	Duration	Results
Tacrine Study Group[21]	n=468	12 week double-blind, placebo-controlled, parallel-group study	In comparing the efficacy and safety of tacrine with placebo in patients with AD: • After 12 weeks, dose-related improvement was significant on the ADAS cognitive component (P=0.014), clinician-rated Clinician Global Impression Change (CGIC) (P=0.016), and caregiver-rated CGIC (P=0.028) for patients given tacrine. • Among patients receiving 80mg/day of tacrine, 51% achieved a four-point or greater improvement of the ADAS cognitive component after 12 weeks of treatment. • Reversible asymptomatic transaminase elevations greater than three times of normal occurred in 25% of patients. • Other treatment related adverse events included nausea and/or vomiting (8%), diarrhea (5%), abdominal pain (4%), dyspepsia (3%), and rash (3%).
Rivastigmine in moderately severe AD[22]	n=2,126	Retrospective pooled analysis from 3 randomized, placebo-controlled, double-blind, 6 month trials	In evaluating the effectiveness of rivastigmine in more severe dementia: • Mean ADAS-cog score declined by 6.3 points in the placebo group and increased by 0.2 points in the rivastigmine group (P<0.001). • Clinical benefits were also observed with the MMSE, the six-item progressive deterioration scale, and items of the BEHAV-AD assessed efficacy. • Rivastigmine showed the same pattern of adverse events as in other studies, but the relative risk of dropping out due to adverse events was lower than in subjects with milder AD.
Efficacy and safety of donepezil[23]	n=473	24 week, randomized, double-blind, placebo-controlled, multicenter trial	In evaluating the efficacy, tolerability, and safety of donepezil in mild-moderate Alzheimer's disease: • Out of 473 patients, 80% of placebo patients, 85% of 5mg patients and 68% of 10mg patients completed the study. Those that discontinued due to adverse effects were 7%, 6%, and 16% in the placebo, 5mg and 10mg groups, respectively. • Primary outcome measure was mean change in scores from baseline to endpoint in the ADAS-Cog. Both donepezil doses were statistically better than placebo (p<0.0001). • Global functioning as measured by the CIBIC plus were statistically better for both donepezil groups compared to placebo at endpoint (p<0.005). • Donepezil 5mg and 10mg showed no statistical difference in improvements although numerical trends for improvement were noted in the 10mg dose over the 5mg dose.

Study	Sample	Duration	Results
Efficacy and safety of galantamine vs. placebo[24]	n=653	6 month, double-blind, fixed dose of 24mg or 32mg of galantamine vs. placebo	To evaluate the safety and efficacy of galantamine 24mg, 32mg vs. placebo with mild-moderate AD: • Both doses of galantamine were statistically better than placebo in the mean change in ADAS-Cog from baseline to endpoint ($p<0.0001$). • Patients taking galantamine 24mg had a -0.5 point mean change on the ADAS-Cog scale, while the 32mg group had a -0.8 change. This compares to a +2.4 change for the placebo group. Statistical comparisons between the 24mg group and the 32mg group were not conducted. • Discontinuations due to adverse events were 9%, 14%, and 22% in the placebo, 24mg and 32mg dose groups, respectively.
Galantamine benefits sustained for 36 months[25]	n=194	36 month randomized, double-blind, placebo-controlled trial	To report the long-term cognitive effects of galantamine given continuously for 36 months in mild-moderate AD patients: • Patients treated continuously with galantamine for 36 months increased a mean +/- SE of 10.2 +/- 0.9 points on the AD assessment scale-11-item cognition subscale. This was a substantially smaller cognitive decline (approximately 50%) than that predicted for the placebo group. • Patients discontinuing galantamine therapy before 36 months had declined at a similar rate before discontinuation as those completing 36 months of treatment. • Almost 80% of patients who received galantamine for 36 months seemed to demonstrate cognitive benefits compared with those predicted for untreated patients.
Long-term donepezil treatment[26]	n=565	12 week run-in period study; 156 weeks total duration	In evaluating donepezil's ability to produce worthwhile improvements in disability, dependency, behavioral and psychological symptoms, caregiver psychological wellbeing, or delay in institutionalization: • Cognition averaged 0.8MMSE points better (95% CI 0.5 to 1.2;$p<0.0001$) and functionality 1.0 BADLS points better (0.5 to 1.6;$p<0.0001$) with donepezil over the first 2 years. • No significant benefits were seen with donepezil compared with placebo in institutionalization (42% vs. 44% at 3 years; $p=0.4$) or progression of disability (58% vs. 59% at 3 years; $p=0.4$). • The relative risk of entering institutional care in the donepezil group compared with placebo was 0.97 (95% CI 0.72 to 1.30; $p=0.8$); the relative risk of progression of disability or entering institutional care was 0.96 (95% CI 0.74 to 1.24; $p=0.7$). • Similarly, no significant differences were seen between donepezil and placebo in behavioral and psychological symptoms, caregiver psychopathology, formal care costs, unpaid caregiver time, adverse events or deaths, or between 5 mg and 10 mg donepezil. • Conclusion: Donepezil offers benefits below minimally relevant thresholds. More effective treatments than cholinesterase inhibitors are needed for Alzheimer's disease.

Study	Sample	Duration	Results
Effects of galantamine on caregiver distress and behavioral disturbances[27]	n=978	21 week randomized, double-blind, placebo-controlled study	When evaluating the impact of galantamine on the pattern and evolution of behavioral disturbances in patients with mild-moderate AD, and in looking at caregiver distress related to patients' behavior: • Neuropsychiatric inventory scores worsened with placebo, whereas patients treated with 16 or 24 mg/day of galantamine had no change in total neuropsychiatric inventory scores. • Behavioral improvement in patients symptomatic at baseline ranged from 29% to 48%. Changes were evident in patients receiving 16 and 24 mg/day of galantamine. • High dose galantamine was associated with a significant reduction in caregiver distress.
Donepezil delays nursing home placement[28]	n=1,115	Follow-up of patients previously enrolled in one of three randomized, double-blind, placebo-controlled trials of donepezil, and two subsequent open-label studies.	Data was obtained through interviews with caregivers and through chart reviews of patients previously enrolled in donepezil studies: • Use of donepezil of 5mg/day or more was associated with significant delays in nursing home placement. • A cumulative dose-response relationship was observed between longer-term sustained donepezil use and delay of nursing home placement. • When donepezil was taken at effective doses for at least 9-12 months, conservative estimates of the time gained before nursing home placement were 21.4 months for first-dementia-related nursing home placement and 17.5 months for permanent nursing home placement.
Donepezil and Vitamin E[29]	n=130	1 year retrospective chart review	In order to examine the long-term effects of combination donepezil and vitamin E therapy on patients with AD, a retrospective chart review was performed. Data were compared with the Consortium to Establish a Registry for Alzheimer's Disease database for patients collected prior to the availability of these treatment options. • Patients declined at a significantly lower rate as compared with the Consortium to Establish a Registry for Alzheimer's Disease data. • The long-term combination therapy of donepezil and vitamin E appears beneficial for patients with Alzheimer's disease. • Future prospective studies would be needed to compare combination treatment to vitamin E and donepezil alone.

Study	Sample	Duration	Results
Memantine and donepezil in moderate to severe AD[13]	n=404	24 week double-blind, placebo-controlled U.S. trial	In evaluating the functional, cognitive, and global outcome measures in moderate to severe AD patients receiving ongoing donepezil therapy for at least 6 months, who were given memantine 10mg BID or placebo: • A significantly greater therapeutic effect was observed in the memantine group than in the placebo group on the ADCS-ADL, SIB, and CIBIC-Plus. • Patients receiving memantine in combination with donepezil demonstrated significantly less decline in ADCS-ADL scores compared to patients receiving donepezil/placebo over the 24-week study period (p=0.02). • Patients receiving memantine showed significantly less cognitive decline in SIB scores compared to patients receiving placebo. In fact, therapy with memantine/donepezil resulted in sustained cognitive performance above baseline compared with the progressive decline seen with the donepezil/placebo treatment. • The change in total mean scores favored memantine vs. placebo for the CIBIC-Plus (possible score range, 1-7), 4.41 (0.074) vs. 4.66 (0.075), respectively (p=0.03). • Treatment discontinuations due to adverse events for memantine vs. placebo were 15 (7.4%) vs. 25 (12.4%), respectively.
Donepezil vs. rivastigmine[17]	n=111	12 week multinational, randomized study, open label	In comparing the tolerability and cognitive effects of donepezil (up to 10mg QD) and rivastigmine (up to 6mg BID) in patients with mild-moderate Alzheimer's disease: • More patients taking donepezil completed the study (89.3%) compared to the rivastigmine group (69.1%) p=0.009. • 10.7% of the donepezil group and 21.8% of the rivastigmine group discontinued treatment due to adverse events. • 87.5% of the donepezil patients and 47.3% of the rivastigmine patients remained on the maximum approved dose of each drug at the last study visit. • Both groups showed comparable improvements in the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) administered at weeks 4 and 12.
Galantamine vs. donepezil[18]	n=182	52 week randomized, rater-blinded, parallel-group, multicenter study	When evaluating the long-term efficacy and safety of galantamine 24mg/day and donepezil 10 mg/day in patients with Alzheimer's disease: • The Bristol Activities of Daily Living Scale (primary outcome measure for functionality) total score showed no significant difference between treatment groups in mean change from baseline to week 52. • In terms of cognition, galantamine patients' scores on the MMSE at week 52 did not differ significantly from baseline, whereas donepezil patients' scores deteriorated significantly from baseline (P<0.0005). • The between group difference in MMSE change, which showed a trend for increased effectiveness of galantamine, did not reach statistical significance.

Study	Sample	Duration	Results
			• In the ADAS-cog analysis, between group differences for the total population were not significant, whereas galantamine treated patients with MMSE scores of 12-18 demonstrated an increase (worsening) in the ADAS-cog score of 1.61 +/- 0.80 versus baseline, compared with an increase of 4.08 +/- 0.84 for patients treated with donepezil. • More caregivers of patients receiving galantamine reported reductions in burden compared with donepezil. • Changes from baseline in Neuropsychiatric Inventory were similar for both treatments.
Donepezil vs. galantamine[19]	n=120	12 week randomized, open-label, multinational study	In comparing the ease of use and tolerability of donepezil (up to 10mg QD) and galantamine (up to 12mg BID), and to investigate the effects of both treatments on cognition and activities of daily living: • Physicians and caregivers reported statistically significant greater satisfaction/ease of use with donepezil compared to galantamine at weeks 4 and 12. • Significantly greater improvements in cognition were observed for donepezil versus galantamine on the ADAS-cog at week 12 and at endpoint. • Activities of daily living improved significantly in the donepezil group compared with the galantamine group at weeks 4 and 12 ($P<0.05$). • 46% of galantamine patients reported GI adverse events versus 25% of donepezil patients.
Donepezil vs. galantamine, a meta-analysis[30]	n=3352, 8 studies	Meta-analysis of randomized, placebo-controlled, double-blind trials after 1984	3 donepezil studies and 5 galantamine studies were analyzed. Efficacy was measured using ADAS-Cog or MMSE. • Neither group was considered very efficacious. The majority of patients showed no difference compared to placebo. • There was no difference in efficacy between the groups.
Differential efficacy of treatment with AchEI in patients with mild-moderate AD over 6 months[31]	N=147	6 month open label prospective comparison between donepezil, galantamine, rivastigmine and 45 historical controls	Compare the efficacy between donepezil, galantamine and rivastigmine with a historical retrospective control. • Average doses were donepezil 5.8mg/d, galantamine 14.87 mg/d, rivastigmine 5.87 mg/d. • All 3 groups had better MMSE scores compared to control (donepezil $p<0.001$, galantamine $p<0.01$, rivastigmine $p<0.03$). • There were no statistical differences between the groups on measures of cognitive decline (via MMSE) • There was a heterogeneous response amongst the treated group.

Study	Sample	Duration	Results
Open label comparison of donepezil, galantamine and rivastigmine[32]	N=407	Observational study, 9 months	MMSE, ADL and IADL scores were compared. Doses ranged from 5-10 mg for donepezil, 6-12mg for rivastigmine, and 16-24 mg for galantamine. • 63% were taking donepezil, 32% were taking rivastigmine, and 5% were taking galantamine. • 212 patients completed all 9 months. • There were no differences amongst the three groups in regards to any of the outcome measures. • Discontinuation due to adverse effects was lower in those patients on donepezil (3%) vs. rivastigmine (17%) p=0.01 and vs galantamine (21%) p=0.01.
Open label comparison of donepezil, galantamine and rivastigmine[33]	N=242	6 month open label trial	Outcome measures were the MMSE, ADAS-Cog, ADL and IADL. 70 patients were treated with donepezil, 121 with rivastigmine , and 51 with galantamine. • There were no statistical differences on changes in the MMSE, ADAS-Cog, ADL or IADL measures amongst the 3 groups. • Rivastigmine showed a small numerical advantage (but not statistically) compared to donepezil and galantamine on the ADAS-Cog.
Meta-analysis on treatment of functional impairment looking at any cholinesterase inhibitor[34]	29 trials	Search of MEDLINE, Dissertation abstracts On-Line, PSYCHOINFO, BIOSIS, PubMed, Cochrane controlled trials register from 1/1966-12/2001	Trials included randomized, DBPC, parallel or crossover design, outpatients with mild or moderate Alzheimer's disease. Medications included metrifonate, galantamine, donepezil, tacrine, velnacrine, rivastigmine, eptastigmine, physostigmine patch. Measures included the NPI, ADAS-noncog, ADL and IADLs. • AcheIs improved the NPI statistically better than placebo (95% CI, 0.87-2.57 points). • AcheIs improved the ADAS-noncog measure numerically but not statistically compared to placebo (95% CI, 0.0-0.05 points). • AcheIs improved ADLs numerically but not significantly better than placebo (95% CI, 0.0-0.19 points). • AcheIs improved IADLs statistically compared to placebo (95% CI, 0.01-0.17).
28-week U.S. trial: memantine vs. placebo[35]	n=252	28 week double-blind treatment study	In evaluating functional, cognitive, and global outcome measures in patients with moderate to severe AD who received either memantine 10mg BID or placebo: • A significantly greater effect was observed in the memantine group compared to the placebo group on the ADCS-ADL and SIB. • Memantine patients showed significantly less cognitive decline on the SIB total score compared to placebo-treated patients over the 28-week study period (p=0.002). • There was a significant difference in favor of memantine at week 28 on the CIBIC-Plus using the observed-cases analysis (mean score: 4.74 placebo vs. 4.38 memantine, p=0.025), and a numerical difference at study endpoint in favor of memantine using the last-observed-carried-forward analysis (mean score: 4.73 placebo vs. 4.48 memantine, p=0.064). • Memantine-treated patients showed significantly less functional decline compared to placebo-treated patients over the 28-week study period.

Study	Sample	Duration	Results
12-week memantine Latvia trial: results of the 9M-Best Study[36]	n=166	12 week double-blind, placebo-controlled study	In determining any benefit of memantine when administered to patients with severe dementia, either AD or vascular dementia, by studying functional and global efficacy measures: • Significantly greater improvement was observed in the memantine group compared to the placebo group on the BGP-care dependency subscale and the CGI-C. • Separate analyses of the AD population alone also yielded statistically significant results in favor of patients receiving memantine, by either the last-observed-carried-forward analysis or the observed-cases analysis on both outcome measures. • At study endpoint, memantine patients showed significantly greater functional improvement compared to patients who received placebo, at study endpoint (p=0.012).

Staging Tools Key:
CGI-S: Clinical Global Impression of Severity Scale
CHI-C: Clinical Global Impression of Change Scale
GDS: Global Deterioration Scale
FAST: Functional Assessment Staging Tool

Cognition Efficacy Measures Key:
SIB: Severe Impairment Battery
CIBIC-Plus: Clinician's Interview-Based Impression of Change Plus Caregiver Input
ADCS-ADL: Alzheimer's Disease Assessment Scale Cognitive Subscale
BGP: Behavioral Rating Scale for Geriatric Patients
MMSE: Mini-Mental Status Exam

Additional Evidence

Dose Simplification: Little evidence is available on medication adherence in Alzheimer's Disease. One study that looked at pharmacy claims data suggests the probability of a new user continuing donepezil at 90 days was 0.797 +/- 0.103 and at 180 days was 0.627 +/- 0.124.[37] Additionally, 13.9% of those who continued therapy for at least 180 days showed gaps in treatment of six weeks or more. A study by Jones, et al. [19] assessed physician's and caregiver's satisfaction with once a day donepezil versus twice daily galantamine. They reported statistically significant greater total mean scores for donepezil versus galantamine, particularly on the dosing frequency item of the Physician's and Caregiver's Satisfaction Questionnaires; however, no difference in compliance was noted. The authors reported significantly greater improvement in cognition and activities of daily living with donepezil compared to galantamine at the end of the 12 week study; but it was not clear if the differences in clinical outcomes were due to dosing frequency or other factors.

Stable Therapy:
Additive risk of adverse events may be expected with coadministration of these drugs, or with inadequate washout periods between agents. One report of fatal aspiration pneumonia has been published after initiation of rivastigmine and discontinuation of donepezil with no washout period between therapies.[38] A washout period should be considered, and is usually recommended when switching between cholinesterase inhibitors.

The pharmacological differences among the cholinesterase inhibitors and evidence from comparative studies support a switch strategy when a patient is intolerant to one drug or when a therapeutic dose to one drug cannot be reached.[39] As previously mentioned, one study reported that when switched from donepezil to rivastigmine, about 50% of those who had side-effects or no efficacy with donepezil tolerated or responded well to rivastigmine. In about a third of patients treated with a cholinesterase inhibitor, symptoms will worsen in the first 6 months of initial treatment, and the responsiveness to a second inhibitor is variable.

A post-hoc analysis of a 5-month trial with galantamine showed that patients had similar efficacy outcomes, whether or not they had received prior anticholinesterase therapy, suggesting that a previous failure to respond to another cholinesterase inhibitor did not predict response to galantamine.[40] On the basis of available data, it is suggested that patients not tolerating or not responding to one particular cholinesterase inhibitor may still draw benefits upon switching to another.

There is only limited guidance in the literature on the safety of switching the cholinesterase inhibitors. The maintenance of a therapeutic inhibition of acetylcholinesterase throughout the switching period is desirable and, for both galantamine and rivastigmine, time is needed to reach a therapeutic dose after the start of the titration. More research is needed to establish practice guidelines for switching cholinesterase inhibitors.

Maelicke has studied risks associated with switching from donepezil to galantamine and has created a theoretical model for switching.[41] He stated that galantamine does not cause any long-lived increases in the acetylcholinesterase inhibition produced by the first drug used. Preliminary findings suggest there does not seem to be an urgent need for a washout protocol. This means the same dose escalation profile used for first-time galantamine patients could be used for patients who were exposed previously to other cholinesterase inhibitors. Because the effects of galantamine are rapidly reversible, switching from a previously used cholinesterase inhibitor to galantamine should be easy. The most conservative switch protocols (for use if adverse events occur) suggest a 1 week washout, followed by a daily dose of galantamine 8mg (4mg BID) escalated to 16mg QD (8mg BID) after 4 weeks. Another study found that a 4 day washout of donepezil was equally well tolerated to a 7-day washout when switching to galantamine.[15]

Duration of therapy with cholinesterase inhibitors or memantine is controversial. Although it is clear that responding patients will return to baseline in 9 months it has been shown that without treatment these patients would have worse cognitive skills. Open label extensions have shown benefit for up to 2 years on cognitive functioning. However, the AD2000 trial showed no benefit in time to institutionalization or progress of disability for patients treated with donepezil for up to 5 years.[26]

Impact on Physician Visits: Data is not available relating to Alzheimer's treatments and impact on utilization of physician services. However, some literature is available on Alzheimer's disease and utilization of services. One study by Fillenbaum, et al. looked at the probability and frequency of outpatient visits of patients with Alzheimer's disease and assessed whether stage of illness or institutionalization had any impact.[42] In this Medicare population, the number of patients with AD and a Medicare-reimbursed outpatient visit ranged from 81% to 95% and was not related to stage of dementia or institutional status.[42] Whether AD patients compared to those without AD have more physician visits has not been clearly determined due to questions about diagnosis and identification on claims. Another study showed the onset of AD is not associated with greater use of acute care services nor is the high use of nursing home care offset by fewer ER or hospital encounters.[43] A study evaluated a care consultation multi-component telephone intervention program where healthcare professionals work with patients and caregivers to determine resources within the family of an Alzheimer's patient.[44] Alzheimer's patients in the program felt less embarrassed and isolated because of their memory problems and reported less problems coping with their disease. Intervention patients with more severe impairment had fewer physician visits, were less likely to have an emergency room visit or hospital admission, and had decreased depression and strain.

Wimo, et al,[45] performed a cost analysis of a previously published 28 week efficacy trial.[46] They found that in moderate to severe Alzheimer's disease outpatients the use of memantine was associated with a significantly less amount of total caregiver time vs. placebo (51.5 hours less for the memantine group per month, 95% CI, -95.27 to -7.17, p=0.02). There were fewer patients institutionalized at week 28 in the memantine group (1) compared to the placebo group (5) which was statistically significant (p=0.04). The authors calculated that the overall societal costs were $1089.74/month less with the memantine treated group compared to the placebo group and that this was statistically significant (95% CI, -1954.90 to -224.58, p=0.03).

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this AHFS drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current AL Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the AL Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the AL Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0 - $25 per Rx
$$	$26 -$50 per Rx
$$$	$51-$75 per Rx
$$$$	$76-$100 per Rx
$$$$$	$101-$150 per Rx

Rx = prescription

Table 10. Relative Cost of Alzheimer's Agents

Drug Classification	Generic Name*	Form	Example Brand Name(s)	Brand Cost	Generic Cost
Cholinesterase inhibitor	Donepezil	Oral	Aricept®	$$$	N/A
	Rivastigmine	Oral	Exelon®	$$$$	N/A
	Galantamine	Oral	Razadyne® (formerly Reminyl®), Razadyne ER®	$$$$	N/A
	Tacrine	Oral	Cognex®	$$$$$	N/A
NMDA receptor antagonist	Memantine	Oral	Namenda®	$$$	N/A

* There are no generic or over-the-counter formulations available for any of the medications in this class
N/A = not available

X. Conclusions

All four cholinesterase inhibitors have the same FDA-approved indication for Alzheimer's disease. A review of the pharmacokinetic properties of each agent shows that rivastigmine is the single agent not metabolized by the cytochrome P450 enzyme system, resulting in less potential for pharmacokinetic drug interactions. Tacrine posses significant disadvantages over other cholinesterase inhibitors due to its association with high rates of liver transaminase level elevations, and its four times a day dosing schedule.

Clinical data from trials listed above suggest that donepezil is better tolerated than rivastigmine or galantamine. Efficacy data on cognitive function from trials comparing the cholinesterase inhibitors have shown that they are equally effective. Better designed head-to-head studies are needed between these agents to fully evaluate their comparative efficacy. Currently, the agents in this class (excluding tacrine) remain comparable in efficacy and all show a modest improvement in the rate of decline in cognitive function.

A significant amount of literature supports use of the cholinesterase inhibitors as first-line agents for mild-moderate AD. Use of donepezil, galantamine or rivastigmine in the treatment of cognitive and neuropsychiatric complications of Alzheimer's disease provides comparable outcomes. All acetylcholinesterase inhibitor brand products within the class reviewed are comparable in efficacy and none offer any efficacy related significant advantage. Tacrine possesses an extensive adverse effect profile and should not be used as a first-line agent. There are no generic or over-the-counter products within the cholinesterase inhibitor class.

Memantine has FDA approval for moderate to severe stages. It has also been studied as add-on therapy with donepezil with results suggesting better tolerability than monotherapy. The addition of memantine to any current cholinesterase regimen may confer additional benefit, particularly in the area of tolerability and caregiver burden.

XI. Recommendations

Alabama Medicaid should work with manufacturers of brands of cholinesterase inhibitors, excluding tacrine, on cost proposals so that at least one brand cholinesterase inhibitor is selected as a preferred agent.

No brand tacrine product is recommended for preferred drug status, regardless of cost.

No brand NMDA receptor antagonist is recommended for preferred drug status, regardless of cost.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antidepressants
AHFS Class 281604
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I. Overview

Antidepressants are used in the management of a variety of psychiatric disorders including mood disorders, eating disorders, premenstrual dysphoric disorders, and anxiety disorders. Anxiety disorders include obsessive-compulsive disorder, panic disorder, social anxiety disorder, and post-traumatic stress disorder. A mood disorder is defined as a disturbance in mood that is severe enough to impair a person's social, academic, or occupational functioning for a specific duration of time.[1] Major depressive disorder and dysthymic disorder are two examples of mood disorders. Some antidepressants have also been used in non-psychiatric conditions, such as diabetic peripheral neuropathy and nocturnal enuresis in children.

Treatment for psychiatric disorders includes psychotherapy, pharmacotherapy, or the combination of the two. The decision to implement psychotherapy is dependent upon patient willingness and severity of illness. Despite the variety of pharmacologic options available, all antidepressants appear to be equally efficacious for mood disorders. Therefore, initial treatment should depend on the individual's overall medical condition and current medication profile.[2] Pharmacology, tolerability, and safety profiles differ among these classes and among individual agents. However, for all antidepressants, the Food and Drug Administration (FDA) requires manufacturers to include a black-box warning notifying prescribers of the potential for antidepressants to increase suicidal thoughts in children and adults.[3]

The antidepressants can be classified in several ways, such as by chemical structure and/or presumed mechanism of activity. The agents included in this review belong to the following American Hospital Formulary Service (AHFS) categories:[4]

- Monoamine Oxidase Inhibitors (MAOIs)
- Selective-serotonin Reuptake Inhibitors (SSRIs)
- Serotonin Modulators
- Tricyclics and Other Norepinephrine-reuptake Inhibitors
- Antidepressants, Miscellaneous

Table 1 lists the agents included in this review. This review encompasses all dosage forms and strengths.

Table 1. Antidepressants Included in this Review

Generic Name	Formulations	Example Brand Name(s)
Monoamine Oxidase Inhibitors		
Isocarboxazid	Tablets	Marplan®
Phenelzine	Tablets	Nardil®
Tranylcypromine	Tablets	Parnate®
Selective-serotonin Reuptake Inhibitors		
Citalopram	Solution, tablets	Celexa®*
Escitalopram	Solution, tablets	Lexapro®
Fluoxetine	Capsules, solution, tablets	Prozac®*, Rapiflux®
	Delayed-release capsules	Prozac Weekly®
	Capsules	Sarafem®
Fluoxetine and olanzapine	Capsules	Symbyax®

Generic Name	Formulations	Example Brand Name(s)
Fluvoxamine	Tablets	Luvox®*^
Paroxetine HCl	Suspension (no generic), tablets	Paxil®*
	Controlled-release tablets	Paxil CR®
Paroxetine mesylate	Tablets	Pexeva®
Sertraline	Oral concentrate solution, tablets	Zoloft®
Serotonin Modulators		
Nefazodone	Tablets	Serzone®*^
Trazodone	Tablets	Desyrel®*
Tricyclics and Other Norepinephrine-reuptake Inhibitors		
Amitriptyline	Tablets	Elavil®*^, Vanatrip®*
Amitriptyline and chlordiazepoxide	Tablets	Limbitrol®*, Limbitrol DS®*
Amitriptyline and perphenazine	Tablets	Etrafon®*, Etrafon A®*, Etrafon Forte®*, Triavil®*
Amoxapine	Tablets	Asendin®*
Clomipramine	Capsules	Anafranil®*
Desipramine	Tablets	Norpramin®*
Doxepin	Capsules, cream, oral concentrate	Adapin®*, Sinequan®*, Prudoxin®, Zonalon®
Imipramine hydrochloride	Tablets	Tofranil®*
Imipramine pamoate	Capsules	Tofranil-PM®
Maprotiline	Tablets	Ludiomil®*
Nortriptyline	Capsules, solution	Aventyl®*, Pamelor®*
Protriptyline	Tablets	Vivactil®
Trimipramine	Capsules	Surmontil®
Miscellaneous Antidepressants		
Bupropion	Extended-release tablets, sustained-release tablets, tablets	Wellbutrin®*, Wellbutrin SR®*, Wellbutrin XL®
Duloxetine	Delayed-release capsules	Cymbalta®
Mirtazapine	Orally disintegrating tablets, tablets	Remeron®*, Remeron SolTab®*
Venlafaxine	Extended-release capsules, tablets	Effexor®, Effexor XR®

*Generic is available in at least one dosage form or strength.
^Brand is no longer available.

II. Evidence Based Medicine and Current Treatment Guidelines

Table 2. Treatment Guidelines for Certain Psychiatric Disorders

Clinical Guideline	Recommendation
American Psychiatric Association (APA): Practice guideline for the treatment of patients with **major depressive disorder (MDD)**[2]	**Acute** **First line**: SSRIs, desipramine, nortriptyline, bupropion, venlafaxine. Selection is based first on the safety and tolerability of the agents for the individual patient, then on patient preference, clinical data, and cost. **Second line**: MAOIs, restricted to patients unresponsive to other options. **Continuation** Continue therapy to prevent relapse. **Maintenance** Continue therapy that was effective in the acute and continuation

Clinical Guideline	Recommendation
	phases at the same dose. **Duration of treatment:** Adequate trial of therapy requires 4 to 6 weeks of treatment before judging efficacy.[5]
Consensus Statement from the International Consensus Group on Depression and Anxiety: **generalized anxiety disorder (GAD)**[6]	**First line:** Antidepressants–SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs) or least-sedating TCAs. **Second line:** Buspirone **Adjunct therapies:** • Benzodiazepines: consider as first-line therapy agent in an acute anxiety reaction. Use as adjunct agent in acute exacerbations of GAD or sleep disturbances during the initiation of antidepressant therapy. Patient should be stabilized on antidepressant therapy for > 4 weeks before benzodiazepines are slowly tapered (over 4-8 weeks). • Hydroxyzine: consider use in acute anxiety states.
Consensus Statement from the International Consensus Group on Depression and Anxiety: **panic disorder**[7]	**Acute** **First line:** SSRIs, initiated at low dose. **Second line:** Concomitant use of a benzodiazepine for a limited period (< 8 weeks) may be considered to help initiate treatment with a SSRI. **Maintenance** Limited evidence suggests that once patient is in full remission, the therapeutic dose may be reduced slowly. **Second line (non-responders):** If patient fails to respond at the maximum tolerated dose of a SSRI, or if partial response was observed and the SSRI well tolerated, switch to another SSRI. If SSRI not tolerated, initiate trial with a benzodiazepine or tricyclic antidepressant (TCA). **Third line:** Monoamine oxidase inhibitor (MAOI) or valproate. **Duration of treatment:** 8 to 12 weeks of treatment is considered an adequate trial. If remission is maintained, consider stopping treatment after 12-24 months.
American Psychiatric Association (APA): Practice guideline for the treatment of **patients with acute stress disorder and posttraumatic stress disorder (PTSD)**[8]	**First line:** SSRIs. **Second line**: TCAs and MAOIs. Concomitant use of a benzodiazepine in reducing anxiety and improving sleep. **Third line:** Second generation antipsychotic medications (e.g., olanzapine, quetiapine, risperidone). Anticonvulsant medications (e.g., divalproex, carbamazepine, topiramate, lamotrigine), alpha-2-adrenergic agonists, and beta-adrenergic blockers may also be helpful in treating specific symptom clusters in individual patients. **Duration of treatment:** Adequate trial of therapy requires 3 months of treatment. If treatment is effective and remission maintained, duration of therapy may be extended to 12 months or longer.[9]

Clinical Guideline	Recommendation
The Expert Consensus Guideline Series: Treatment of **obsessive-compulsive disorder (OCD)**[10]	**First line (mild OCD, or young patients):** Cognitive behavior therapy (CBT) alone if mild OCD **Second line (more severe):** CBT plus a serotonin receptor inhibitor, or a serotonin receptor inhibitor alone (guideline specifically lists clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline). Generally clomipramine is used after failure of 2-3 trials of the other selective-serotonin reuptake inhibitors.[11] **Third line:** Venlafaxine, MAOIs, clonazepam **Duration of treatment:** It is recommended to wait 8-13 weeks before making changes to the medication regimen.
Consensus Statement from the International Consensus Group on Depression and Anxiety: **social anxiety disorder (SAD)**[12]	**Pharmacological treatment recommendation**: SSRI. Most studies conducted with paroxetine. Dose should be initiated at 20 mg/day for 2-4 weeks and then titrated to obtain a response. **Duration of treatment:** Adequate trial of therapy requires 6 to 8 weeks of treatment. If treatment is effective and remission maintained, minimum duration of therapy is 12 months. Note: there is no clinical evidence that benzodiazepines, TCA, or β-blockers as a class are effective for treatment of social anxiety disorder.
American College of Obstetricians and Gynecologists: **premenstrual syndrome**[13]	**First line:** Lifestyle changes in diet and exercise, are recommended to initially control symptoms. However, no controlled clinical trials have been conducted to support these interventions. Limited data exists to suggest Vitamin B_6, calcium carbonate, spironolactone, and oral contraceptives may be useful. **Second line**: SSRIs (sertraline and fluoxetine have been studied the most). **Third line**: Clomipramine, alprazolam **Fourth line**: Leuprolide
American Psychiatric Association (APA): Practice guideline for the treatment of patients with **eating disorders**[14]	**First line:** Nutritional rehabilitation and counseling should be initiated to promote weight gain. **Second line:** Ongoing psychotherapy and medication management should be used to prevent a relapse or to treat co-morbid conditions (such as depression or OCD). • SSRIs • Use TCAs and MAOIs with caution in bulemia patients at high risk for suicide attempts. • Avoid MAOIs in patients with chaotic binge eating and purging.

III. Indications

Table 3a. FDA-Approved Indications for the Monoamine Oxidase Inhibitors[15-17]

Generic Name	Indication
Isocarboxazid	Treatment of depression. Isocarboxazid is not to be considered as an antidepressant of first choice in the treatment of newly diagnosed depressed patients with prominent endogenous features.
Phenelzine	Effective in depressed patients clinically characterized as "atypical", "nonendogenous," or "neurotic." These patients often have mixed anxiety, depression and phobic or hypochondriacal features. There is less conclusive evidence of usefulness in severely depressed patients with endogenous features. Phenelzine sulfate is rarely the first antidepressant drug used. Rather, it is more suitable for use with patients who have failed to respond to the drugs more commonly used for these conditions.
Tranylcypromine	For the treatment of Major Depressive Episode Without Melancholia. Tranylcypromine should be used in adult patients who can be closely supervised. It should rarely be the first antidepressant given. Rather, the drug is suited for patients who have failed to respond to the drugs more commonly administered for depression.

Table 3b. FDA-Approved Indications for the Selective-serotonin Reuptake Inhibitors[18-27]

Generic Name	Indication
Citalopram	Depression
Escitalopram	Generalized anxiety disorder (GAD) Major depressive disorder (MDD)
Fluoxetine	Bulimia nervosa Major depressive disorder (MDD) Obsessive-compulsive disorder (OCD) Panic disorder (with or without agoraphobia) Premenstrual dysphoric disorder (PMDD)
Fluoxetine + olanzapine	Treatment of depressive episodes associated with bipolar disorder
Fluvoxamine	Obsessive-compulsive disorder (OCD)
Paroxetine hydrochloride	Generalized anxiety disorder (GAD) Major depressive disorder (MDD) Obsessive-compulsive disorder (OCD) Panic disorder (with or without agoraphobia) Posttraumatic stress disorder (PTSD) Social anxiety disorder (SAD) Premenstrual dysphoric disorder (PMDD)
Paroxetine mesylate	Depression Obsessive-compulsive disorder (OCD) Panic disorder
Sertraline	Major depressive disorder (MDD) Obsessive-compulsive disorder (OCD) Panic disorder Posttraumatic stress disorder (PTSD) Premenstrual dysphoric disorder (PMDD) Social anxiety disorder (SAD)

Table 3c. FDA-Approved Indications for the Serotonin Modulators [28, 29]

Generic Name	Indication
Nefazodone	Treatment of depression
Trazodone	Treatment of depression

Table 3d. FDA-Approved Indications for the Tricyclic Antidepressants and Other Norepinephrine-reuptake Inhibitors[28]

Drug Name	Indication(s)
Clomipramine	Obsessive-compulsive disorder, delusional disorder
Amitriptyline Amoxapine Desipramine Doxepin Imipramine Maprotiline Nortriptyline Protriptyline Trimipramine	Major depressive disorder
Amitriptyline Chlordiazepoxide Doxepin	Mixed anxiety and depressive disorder
Amitriptyline Perphenazine	Depression-schizophrenia, mixed anxiety and depressive disorder
Doxepin	Pruritis
Imipramine	Pediatric nocturnal enuresis

Table 3e. FDA-Approved Indications for the Miscellaneous Antidepressants[30-34]

Drug Name	Indication(s)
Bupropion	Major depressive disorder Smoking cessation assistance
Duloxetine	Major depressive disorder Diabetic peripheral neuropathic pain
Mirtazapine	Major depressive disorder
Venlafaxine	Major depressive disorder Generalized anxiety disorder Social anxiety disorder

IV. Pharmacokinetics

Monoamine Oxidase Inhibitors[4,27]

Limited information is available regarding the pharmacokinetics of MAOIs, particularly isocarboxazid and phenelzine. MAOIs are well absorbed orally. The onset of pharmacologic action of tranylcypromine is more rapid than that of the hydrazine-derivative MAOIs with peak levels of tranylcypromine and phenelzine reached in 2 and 3 hours, respectively. Following a single oral dose of tranylcypromine in a limited number of depressed patients with normal renal and hepatic function, the volume of distribution ranged from 1.1-5.7 L/kg. In these patients, the elimination half-life averaged 2.5 hours (range: 1.3-3.2 hours). The hydrazine MAOIs, isocarboxazid and phenelzine, are thought to be metabolized to active metabolites, which are excreted in the urine. Maximal inhibition of MAO occurs within 5-10 days. The clinical effects of phenelzine may continue for up to 2 weeks after discontinuation of therapy. Following discontinuance of tranylcypromine, the drug is excreted within 24 hours; however, urinary tryptamine concentrations, which are used to measure MAO activity, return to normal within 72-120 hours.

Table 4a. Pharmacokinetic Parameters of Single Entity Selective-serotonin Reuptake Inhibitors[18-27]

Drug	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Mechanism of action	Inhibits CNS neuronal reuptake of serotonin	S-enantiomer of citalopram. Inhibits CNS neuronal reuptake of serotonin; minimal or no effect on norepinephrine or dopamine reuptake	Inhibits CNS neuronal reuptake of serotonin; minimal or no effect on norepinephrine or dopamine reuptake	Inhibits CNS neuronal reuptake of serotonin; minimal or no effect on norepinephrine or dopamine reuptake	Inhibits CNS neuronal reuptake of serotonin	Inhibits CNS neuronal reuptake of serotonin; minimal or no effect on norepinephrine or dopamine reuptake
Bioavailability (%)	≈ 80	80	No data	53	100	No data
Protein binding (%)	≈ 80	≈ 56	≈ 94.5	≈ 80	≈ 93-95	98
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic; extensive first-pass metabolism
Active metabolites	demethylcitalopram (DCT), didemethylcitalopram (DDCT), citalopram-N-oxide, and a deaminated propionic acid derivative	S-DCT and S-didemethylcitalopram (SDDCT)	norfluoxetine and a number of other unidentified metabolites	At least 9 inactive metabolites have been identified	Inactive metabolites	N-desmethylsertraline shown to be substantially less active than sertraline
Elimination	Renal (20%), fecal	Renal (7%)	Hepatic	Renal (94%)	Renal (64%), fecal (36%)	Renal (40-45%), fecal (40-45%)
Half-Life (hours)	≈ 35	27-32	24-384	13.6-15.6	21 12-20*	26-104

* paroxetine controlled-release

Table 4b. Pharmacokinetic Parameters of Combination Selective-serotonin Reuptake Inhibitors[22]

Drug	Olanzapine	Fluoxetine
Mechanism of action	Exact mechanism unknown, believed to act as an antagonist of dopamine and serotonin (type 2). Also believed to inhibit muscarinic, adrenergic, and histaminic receptors	Inhibits CNS neuronal reuptake of serotonin; minimal or no effect on norepinephrine or dopamine reuptake
Bioavailability (%)	>57	No data
Protein binding (%)	93	≈ 94.5
Metabolism	Glucuronidation and CYP 450-mediated oxidation	Hepatic
Active metabolites	Inactive metabolites:10-N-glucuronide and 4′-N-desmethyl olanzapine	Norfluoxetine and a number of other unidentified metabolites
Elimination	Renal (57%)	Hepatic
Half-Life (hours)	21-54	24-384

Table 4c. Pharmacokinetic Parameters of the Serotonin Modulators[27, 28]

	Nefazodone	Trazodone
Mechanism of Action		
	Nefazodone potently antagonizes the 5-HT_2 receptors and inhibits both serotonin and norepinephrine reuptake while lacking affinity for muscarinic cholinergic and H_1-histaminic receptors.	The mechanism of action of trazodone is not fully understood. In animals, it selectively inhibits serotonin uptake by brain synaptosomes and potentiates the behavioral changes induced by the serotonin precursor, 5-hydroxytryptophan.
Pharmacokinetics		
Bioavailability	20% Food delays absorption and decreases systemic bioavailability by about 20%.	65% Absorption may be up to 20% higher when the drug is taken with food rather than on an empty stomach.
Protein binding	99%	89-95%
Metabolism	N-dealkylation and aliphatic and aromatic hydroxylation; nefazodone undergoes extensive first pass metabolism to 3 metabolites.	Extensively metabolized in the liver by oxidation and hydroxylation. Cytochrome P450 3A4 metabolizes trazodone to an active metabolite. Cytochrome P450 2D6 is also involved in its metabolism.
Active Metabolites	Yes; hydroxynefazodone (HO-NEF), meta-chlorphenylpiperazine (mCPP), and a triazole-dione metabolite.	Yes; meta-chlorophenylpiperazine.
Elimination	Fecal (20-30%), renal (55%)	Feces (21%), renal (70-75%), urine (<1%)
Half-Life	1.9-5.3 hours	Initial half-life of 3-6 hours, followed by a slower phase half-life of 5-9 hours

Pharmacokinetic Parameters of the Tricyclic Antidepressants and Other Norepinephrine-reuptake Inhibitors[4,28,35-38]

As a group, the tricyclic antidepressants and heterocyclic antidepressants are extensively metabolized in the liver by CYP450. Multiple pathways of CYP450 are involved with 2D6 and 1A2 playing the most prominent role and 2C19 playing a lesser role.

Of note is the fact that amitriptyline is metabolized to nortriptyline and imipramine is metabolized into desipramine. Other members of this class with active metabolites are clomipramine, amoxapine, doxepin, and maprotiline.[35]

Table 4d. Pharmacokinetic Parameters of the Tricyclic Antidepressants and Other Norepinephrine-reuptake Inhibitors[4,28,35-38,43]

Drug	F	Metabolism	Metabolites	Protein Binding	Half-Life
Amitriptyline	48%	Liver, CYP2D6/1A2/2C19	Nortriptyline[±] 10-hydroxy-mortriptyline[±]	90-97%	9-46 hours
Amoxapine	35%	Liver, CYP2D6/1A2	8-hydroxyamoxapine 7-hydroxyamoxampine[±]	90%	8-30 hours
Clomipramine	50%	Liver, CYP2D6/1A2/2C19	Desmethylclomipramine[±]	97%	20-24 hours
Desipramine	40%	Liver, CYP2D6	2-hydroxydesipramine[±]	73-92%	11-46 hours
Doxepin	30%	Liver, CYP2D6/1A2	Desmethyldoxepin[±]	68-82%	8-36 hours
Imipramine	42%	Liver, CYP2D6/1A2/2C19	Desipramine[±], 2-hydroxyimipramine[±] 2-hydroxydesipramine[±]	63-96%	6-34 hours
Maprotiline	85%	Liver, CYP 2D6	Desmethylmaprotiline[±] Maprotiline-N-oxide[±]	88%	28-105 hours
Nortriptyline	51%	Liver, CYP2D6	10-hydroxynortriptyline[±]	87-95%	16-88 hours
Protriptyline	82%	Liver, CYP2D6	No clinically important metabolites	90-94%	54-198 hours
Trimipramine	40%	Liver, CYP2D6	Desmethyltrimipramine[±]	94-96%	7-40 hours

F=Bioavailability

Table 4e. Pharmacokinetic Parameters of the Miscellaneous Antidepressants[28,30-34]

Drug	F	Metabolism	Metabolites	Excretion	Half-Life
Bupropion	N/A	Liver, CYP2B6	Hydroxybupropion[±] Erythrohydrobupropion[±] Threohydrobupropion[±]	Renal (87%); fecal (10%)	14h but 21h w/chronic dosing, metabolites 22h, 33h, 37h
Duloxetine	>70%	Liver, CYP2D6/1A2	Desmethyl duloxetine[±] Hydroxylated metabolite[±]	Renal (77%); fecal (15%)	11-16h
Mirtazapine	50%	Liver, CYP2D6/1A2/ 3A4	Demethylmirtazapine[±] 8-Hydroxy metabolite N-Desmethyl metabolite N-Oxide metabolite	Renal (75%); fecal (15%)	20-40h, Demethyl-mirtazapine 25h
Venlafaxine	12%[¶] 45%[*]	Liver, CYP2D6	O-desmethylvenlafaxine[±] N-desmethylvenlafaxine[±] N,O-didesmethylvenlafaxine[±]	Renal (36-60%); urinary (38-60%)	5h, O-desmethyl-venlafaxine 11h

F=Bioavailability [¶] Effexor® [*]Effexor XR® [±]Active metabolite h = hours

V. Drug Interactions

Monoamine Oxidase Inhibitors (MAOIs)

MAOIs should not be administered in combination with any of the following: other MAOIs, SSRIs, or dibenzazepine derivatives; sympathomimetics (including amphetamines), central nervous system depressants (including narcotics and alcohol); antihypertensive, diuretic, antihistaminic, sedative or anesthetic drugs; bupropion; buspirone; dextromethorphan; meperidine; cheese or other foods with high tyramine content; or excessive quantities of caffeine.[27] Table 5a lists significant drug interactions with MAOIs. Hypertensive crisis can occur when MAOIs are administered concomitantly with foods high in tyramine content or with sympathomimetic medications.

Table 5a. Significant Drug Interactions with Monoamine Oxidase Inhibitors[27]

Precipitant Drug	Object Drug	Description
Methylphenidate	MAOIs	Coadministration may cause hypertensive crisis.
Metrizamide	MAOIs	Discontinue MAOIs at least 48 hours before myelography and do not resume for at least 24 hours post procedure because of the decrease of the seizure threshold.
MAOIs	Anesthetics	Patients taking MAOIs should not undergo elective surgery requiring general anesthesia. Do not give cocaine or local anesthesia containing sympathomimetic vasoconstrictors. Keep in mind the possible combined hypotensive effects of MAOIs and spinal anesthesia. Discontinue the MAOI at least 10 days before elective surgery.
MAOIs	Antidepressants	Do not administer MAOIs together with or immediately following these agents. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible fluctuations of vital signs, and mental status changes that include extreme agitation and confusion progressing to delirium and coma). Do not administer MAOIs together or in rapid succession with other MAOIs.
MAOIs	Antidiabetic agents	MAOIs may potentiate the hypoglycemic response to insulin or sulfonylureas and delay recovery from hypoglycemia.
MAOIs	Barbiturates	Give barbiturates at a reduced dose with MAOIs.
MAOIs	Beta-blockers	Bradycardia may develop during concurrent use of certain MAOIs and beta-blockers.
MAOIs	Bupropion	The concurrent use of a MAOI and bupropion is contraindicated. Allow at least 14 days between discontinuation of a MAOI and initiation of bupropion treatment.
MAOIs	Buspirone	Do not take isocarboxazid in combination with buspirone. Several cases of elevated blood pressure have occurred. Allow at least 10 days between discontinuation of isocarboxazid and institution of buspirone.
MAOIs	Carbamazepine	Hypertensive crises, severe convulsive seizures, coma, or circulatory collapse may occur in patients receiving such combinations.
MAOIs	Cyclobenzaprine	Because cyclobenzaprine is structurally related to the tricyclic antidepressants, use with caution with MAOIs.
MAOIs	Dextromethorphan	Hyperpyrexia, abnormal muscle movement, psychosis, bizarre behavior, hypotension, coma, and death have been associated with this combination.

Precipitant Drug	Object Drug	Description
MAOIs	Guanethidine	MAOIs may inhibit the hypotensive effects of guanethidine.
MAOIs	Levodopa	Hypertensive reactions occur if levodopa is given to patients receiving MAOIs.
MAOIs	Meperidine	Coadministration or use within 2 to 3 weeks of one another may result in agitation, seizures, diaphoresis, and fever and progress to coma, apnea, and death. Adverse reactions are possible weeks after MAOI withdrawal. Avoid this combination; administer other narcotic analgesics with caution.
MAOIs	Methyldopa	Coadministration may cause loss of blood pressure control or signs of central stimulation (e.g., excitation, hallucinations).
MAOIs	Rauwolfia alkaloids	MAOIs inhibit the destruction of serotonin and norepinephrine, which are believed to be released from tissue stores by rauwolfia alkaloids. Exercise caution when rauwolfia is used concomitantly with MAOIs.
MAOIs	Sulfonamide	Coadministration may cause sulfonamide or MAOI toxicity.
MAOIs	Sumatriptan	Systemic exposure to sumatriptan may be increased, producing toxicity.
MAOIs	Sympathomimetics	The MAOIs' potentiation of indirect- or mixed-acting sympathomimetic substances, including anorexiants, may result in severe headache, hypertension, high fever, and hyperpyrexia, possibly resulting in hypertensive crisis; avoid coadministration.
MAOIs	Thiazide diuretics	Exaggerated hypotensive effects may result from concurrent use.
MAOIs	L-Tryptophan	Coadministration may result in hyperreflexia, confusion, disorientation, shivering, myoclonic jerks, agitation, amnesia, delirium, hypomanic signs, ataxia, ocular oscillations, and Babinski signs.

Selective-serotonin Reuptake Inhibitors (SSRIs)

SSRIs used in conjunction with another highly plasma protein-bound drug may affect the concentration of either the SSRI or the other drug and result in drug interactions. When administered with other serotonergic medications, SSRIs have the potential to cause serotonin syndrome, which results from over stimulation of the central and peripheral serotonin receptors and is characterized by nausea, vomiting, flushing, and diaphoresis. In more severe cases, hyperreflexia, myoclonus, muscular rigidity, hyperthermia and autonomic instability may occur. Table 5b lists significant drug interactions for the SSRIs.

Table 5b. Significant Drug Interactions for Selective-serotonin Reuptake Inhibitors[39]

Precipitant Drug	Significance Level	Object Drug	Mechanism
Activated charcoal, charcoal	2	Citalopram, fluoxetine	Charcoal reduces the GI absorption of ingested drugs and absorbs enterohepatically circulated drugs.
Carbamazepine	2	Fluoxetine	Unknown. However, fluoxetine is known to inhibit the metabolism of other drugs, suggesting that this may be the mechanism.
Carbamazepine	2	Sertraline	Increased metabolism (CYP3A4) of sertraline is suspected.
Clozapine	1	Citalopram, fluoxetine, fluvoxamine, sertraline	Certain SSRIs inhibit clozapine hepatic metabolism.
Cyclosporine	2	Fluoxetine, fluvoxamine, paroxetine, sertraline	Inhibition of cyclosporine metabolism (CYP3A4)
Cyproheptadine	2	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Serotonin reuptake inhibitors have serotonergic activity and cyproheptadine is a serotonin antagonist. This activity may occur at the receptor level.
Grapefruit*	1	Fluvoxamine	Inhibition of fluvoxamine intestinal metabolism (CYP3A4) or altered p-glycoprotein-mediated transport by grapefruit juice is suspected.
Grapefruit*	1	Sertraline	Inhibition of sertraline metabolism (CYP3A4) is suspected.
Hydantoins (ethotoin, fosphenytoin, mephenytoin, phenytoin)	2	Fluoxetine	Inhibition of hydantoin metabolism by fluoxetine.
Hydantoins (ethotoin, fosphenytoin, phenytoin)	2	Fluvoxamine	Inhibition of hydantoin metabolism (CYP2C9 and CYP2C19) is suspected.
Hydantoins (ethotoin, fosphenytoin, mephenytoin, phenytoin)	2	Sertraline	Possible inhibition of hydantoins by sertraline.
MAO Inhibitors (isocarboxazid, phenelzine, selegiline, tranylcypromine)	1	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Possibly rapid, excessive accumulation of serotonin.
Methadone (methadone)	2	Fluvoxamine	Fluvoxamine may inhibit the hepatic metabolism of methadone.

Precipitant Drug	Significance Level	Object Drug	Mechanism
NSAIDs (diclofenac, etodalac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin)	2	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Unknown.
Phenothiazines (chlorpromazine, fluphenazine, mesoridazine, methotrimeprazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, thioridazine, trifluoperazine)	2	Paroxetine	Decreased metabolism (CYP2D6) of the phenothiazine.
Phenothiazines (thioridazine)	1	Fluoxetine	Fluoxetine may inhibit the metabolism (CYP2D6) of thioridazine.
Phenothiazines (thioridazine)	1	Fluvoxamine	Inhibition of thioridazine metabolism is suspected.
Pimozide	1	Citalopram, sertraline	Unknown.
Propafenone	2	Fluoxetine, paroxetine, sertraline	Certain serotonin reuptake inhibitors may inhibit the metabolism (CYP2D6) of propafenone.
Risperidone	1	Fluoxetine, paroxetine, sertraline	Inhibition of risperidone metabolism (CYP2D6) by fluoxetine and paroxetine is suspected; possible rapid accumulation of serotonin in the CNS.
Ritonavir	2	Fluoxetine	Fluoxetine and ritonavir may inhibit the metabolism (CYP2D6) of each other.
Ropivacaine	2	Fluvoxamine	Inhibition of ropivacaine metabolism (CYP1A2) by fluvoxamine.
Selective 5-HT1 Receptor Agonists (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)	2	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Rapid accumulation of serotonin in the CNS may occur.
Sibutramine	1	Fluoxetine, fluvoxamine, paroxetine, sertraline	The serotonergic effects of these agents may be additive.

Precipitant Drug	Significance Level	Object Drug	Mechanism
St. John's Wort	2 (1*)	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Possible additive serotonin reuptake inhibition.
Sympathomimetics (amphetamine, benzphetamine, dextroamphetamine, diethylpropion, methamphetamine, phendimetrazine, phentermine)	1	Fluoxetine, fluvoxamine, paroxetine	Unknown.
Tacrine	2	Fluvoxamine	Possibly inhibition of tacrine metabolism (cytochrome P450 1A2) by fluvoxamine.
Theophyllines (aminophylline, oxtriphylline, theophylline)	2	Fluvoxamine	Fluvoxamine inhibits the hepatic metabolism (CYP1A2) of theophylline.
Tizanidine	2	Fluvoxamine	Inhibition of tizanidine metabolism (CYP1A2) by fluvoxamine is suspected.
Tramadol	2	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	The serotonergic effects of these agents may be additive.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Fluoxetine	Fluoxetine may inhibit TCA hepatic metabolism.
Tricyclic antidepressants (amitriptyline, clomipramine, imipramine, trimipramine)	2	Fluvoxamine	Fluvoxamine may inhibit the oxidative metabolism (cytochrome P450 2D6) of TCA.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Sertraline	Probable inhibition of TCA hepatic metabolism (CYP2D6).

Precipitant Drug	Significance Level	Object Drug	Mechanism
Tricyclic antidepressants (amitriptyline, desipramine, imipramine, nortriptyline)	2	Paroxetine	Paroxetine may inhibit the metabolism of certain TCAs in some patients (e.g., extensive metabolizers of sparteine) and may increase metabolism in some patients (e.g., poor metabolizers of sparteine).

Significance Level 1: Major severity
Significance Level 2: Moderate severity
* Indexed in Herbal Interactions Facts; given highest level "Avoid"

Table 5c. Significant Drug Interactions for the Serotonin Modulators[40]

Precipitant Drug	Object Drug	Description
Anesthetics, general	Nefazodone	Little is known about the potential for interactions between nefazodone and general anesthetics. Prior to elective surgery, discontinue nefazodone for as long as clinically feasible.
Sibutramine	Nefazodone	A "serotonin syndrome" including CNS irritability, motor weakness, shivering, myoclonus, and altered consciousness may occur.
Sumatriptan	Nefazodone	A "serotonin syndrome" including CNS irritability, motor weakness, shivering, myoclonus, and altered consciousness may occur in some patients. If co-administration cannot be avoided, start with low dosages and closely monitor the patients. Be prepared to provide supportive care, stop the serotonergic agents, and give antiserotonergic agent (cyproheptadine).
Nefazodone	Alcohol	Although nefazodone did not potentiate the cognitive and psychomotor effects of alcohol in experiments with healthy subjects, the concomitant use of nefazodone and alcohol in depressed patients is not advised.
Nefazodone	Benzodiazepines	Possible increase in CNS-depressant effect. Monitor for increased or decreased CNS effects of benzodiazepines when nefazodone therapy is started or stopped, respectively. An agent that is not eliminated by oxidative metabolism (e.g., lorazepam) may be a suitable alternative.
Nefazodone Buspirone	Buspirone Nefazodone	In healthy volunteers, co-administration resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in Cmax and up to 50-fold in AUC) and statistically significant decreases (50%) in plasma concentrations of the buspirone metabolized 1-pyrimidinylpiperazine. Slight increases in AUC were observed for nefazodone (23%) and its metabolites hydroxylnefazodone (17%) and mCPP (9%). Subjects receiving buspirone and nefazodone experienced side effects such as lightheadedness, asthenia, dizziness, and somnolence. If the 2 drugs are to be used in combination, a low dose of buspirone (eg, 2.5 mg twice daily) is recommended. Base subsequent dose adjustment of either drug on clinical assessment.

Precipitant Drug	Object Drug	Description
Nefazodone Carbamazepine	Carbamazepine Nefazodone	There are reports of elevated serum carbamazepine levels with possible increases in side effects and lower nefazodone levels with possible decreases in efficacy when given concomitantly. Monitor carbamazepine levels and observe the patient for signs and symptoms of carbamazepine side effects or a decrease in therapeutic effect when nefazodone is started or stopped.
Nefazodone	Cisapride	Increased cisapride plasma concentrations with cardiotoxicity may occur.
Nefazodone	Cyclosporine Tacrolimus	Cyclosporine concentrations and toxicity may be increased. Closely monitor trough cyclosporine whole blood concentrations when nefazodone is started or stopped. Adjust the dose of cyclosporine as needed.
Nefazodone	Digoxin	In 1 study, Cmax, Cmin, and AUC of digoxin were increased by 29%, 27%, and 15%, respectively. Plasma level monitoring for digoxin is recommended.
Nefazodone	Haloperidol	Haloperidol apparent clearance decreased by 35% with no significant increase in peak plasma concentration or time to peak.
Nefazodone	HMG-CoA reductase inhibitors (specifically Simvastatin, Atorvastatin, Lovastatin)	There have been rare reports of rhabdomyolysis when these drugs are given concomitantly. Caution should be used and dosage adjustments are recommended if nefazodone is administered with these specific HMG-CoA reductase inhibitors.
Nefazodone	MAOIs	A "serotonin syndrome" including CNS irritability, shivering, myoclonus, and altered consciousness may occur. Do not co-administer. Allow ≥ 1 week after stopping nefazodone before giving a MAOI. After stopping an MAOI, allow ≥ 2 weeks before giving any serotonin reuptake inhibitor.
Nefazodone Propranolol	Propranolol Nefazodone	Co-administration resulted in 30% and 14% reductions in Cmax and AUC of propranolol, respectively, and a 14% reduction in Cmax for the metabolite, 4-hydroxypropranolol. Cmax, Cmin, and AUC of the nefazodone metabolite m-chlorophenylpiperazine were increased by 23%, 54%, and 28%, respectively.
Nefazodone	St. John's Wort	Increased sedative-hypnotic effects may occur.
Trazodone	Alcohol Barbiturates CNS Depressants	Trazodone may enhance the CNS-depressant response to these agents.
Trazodone	Digoxin	Increased serum digoxin levels have been reported to occur in patients receiving concurrent trazodone.
Trazodone	MAOIs	It is not known whether interactions will occur between trazodone and MAOIs. If MAOIs are discontinued shortly before, or are to be given concomitantly with trazodone, initiate therapy cautiously with gradual increase in dosage until optimum response is achieved.
Trazodone	Phenytoin	Phenytoin serum levels were increased with concurrent trazodone therapy.
Trazodone	Warfarin	There have been reports of increased and decreased prothrombin time occurring in patients taking warfarin and trazodone concurrently.

Precipitant Drug	Object Drug	Description
Carbamazepine	Trazodone	Plasma concentrations of trazodone and its active metabolite may be decreased, producing a decrease in therapeutic effect.
Phenothiazines	Trazodone	Elevated trazodone serum concentrations have occurred, increasing the pharmacologic and toxic effects.
SSRIs Venlafaxine	Trazodone	A "serotonin syndrome" including irritability, increased muscle tone, shivering, myoclonus, and altered consciousness may occur.

Table 5d. Significant Drug Interactions for Tricyclic Antidepressants and Other Norepinephrine-reuptake Inhibitors [39]

Precipitant Drug	Significance Level	Object Drug	Mechanism
Tricyclic antidepressants (amitriptyline, imipramine, nortriptyline)	2	Azole antifungal agents: fluconazole, ketoconazole	Inhibition of TCA metabolism is suspected (CYP2C9 by fluconazole; CYP3A4 by ketoconazole).
Tricyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, nortriptyline)	2	Carbamazepine	TCAs may compete with carbamazepine for hepatic microsomal enzyme metabolism. Carbamazepine may induce hepatic metabolism of TCAs.
Tricyclic antidepressants (all)†	2	Cimetidine	Interference with the metabolism of the TCA and decreased first-pass effect resulting in increased bioavailability and higher serum concentrations of the TCA.
Tricyclic antidepressants (all)†	1	Cisapride	Possibly additive prolongation of the QT interval.
Tricyclic antidepressants (all)†	1	Clonidine	Tricyclic antidepressant inhibition of central alpha $_2$ -adrenergic receptors has been postulated, but not conclusively established.
Tricyclic antidepressants (all)†	2	Dicumarol	Impairment of dicumarol's liver degradation by the TCA is possible. Increased dicumarol absorption may also be involved.
Tricyclic antidepressants (all)†	2	Fluoxetine	Fluoxetine may inhibit TCA hepatic metabolism.
Tricyclic antidepressants (amitriptyline, clomipramine, imipramine, trimipramine)	2	Fluvoxamine	Fluvoxamine may inhibit the oxidative metabolism (cytochrome P450 2D6) of TCA.

Precipitant Drug	Significance Level	Object Drug	Mechanism
Tricyclic antidepressants (clomipramine)	2	Grapefruit	Grapefruit products may inhibit intestinal CYP3A3/4 and consequently demethylation of clomipramine.
Tricyclic antidepressants (amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Guanethidine	Inhibition of the uptake of guanethidine into the nerve terminal, its site of action.
Tricyclic antidepressants (all)†	1	MAO inhibitors: isocarboxazid, phenelzine, tranylcypromine	Unknown.
Tricyclic antidepressants (amitriptyline, desipramine, imipramine, nortriptyline)	2	Paroxetine	Paroxetine may inhibit the metabolism of certain TCAs (eg, desipramine) in some patients (eg, extensive metabolizers of sparteine) and may increase metabolism in some patients (eg, poor metabolizers of sparteine).
Tricyclic antidepressants (all)†	1	Quinolones: gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin	Unknown.
Tricyclic antidepressants (all)†	2	Rifamycins: rifabutin, rifampin	Hepatic metabolism of TCAs may be increased.
Tricyclic antidepressants (all)†	2	Sertraline	Probable inhibition of TCA hepatic metabolism (CYP2D6).
Tricyclic antidepressants (all)†	2	St. John's Wort	Hepatic metabolism or drug transporters of TCAs may be increased.
Tricyclic antidepressants (amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Sympathomimetics: dobutamine, dopamine, ephedrine, epinephrine, mephentermine, metaraminol, methoxamine, norepinephrine, phenylephrine	TCAs inhibit the re-uptake of the sympathomimetics in the neuron, increasing or decreasing their sensitivity at the receptor depending on the agent.
Tricyclic antidepressants (desipramine, imipramine, nortriptyline)	2	Terbinafine	Inhibition of TCA metabolism (CYP2D6) by terbinafine is suspected.
Tricyclic antidepressants (all)†	2	Valproic acid (divalproex sodium, valproate sodium, valproic acid)	Decreased first-pass metabolism and inhibition of hepatic metabolism of the TCA.

Precipitant Drug	Significance Level	Object Drug	Mechanism
Tetracyclic antidepressants: maprotiline	1	Cisapride	Possibly additive prolongation of the QT interval.

Significance Level 1: Major severity
Significance Level 2: Moderate severity
† Includes amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine

Miscellaneous Antidepressants

Similar to other classes of antidepressants, these agents are contraindicated with the concurrent use of MAOIs. Bupropion, duloxetine, mirtazapine, or venlafaxine should not be taken within 14 days of MAOI use.[2,5] An appropriate amount of time should be allowed between stopping one of these agents and starting a MAOI. Table 5e highlights some of the pertinent documented drug-drug interactions for bupropion, duloxetine, mirtazapine and venlafaxine.

Table 5e. Significant Drug Interactions for the Miscellaneous Antidepressants[28,30-34]

Affected Drug(s)	Affected By	Mechanism	Reasons/Results/Significance
Bupropion	Orphenadrine, dyclophosphamide, thiotepa	CYP2B6 metabolism	In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore it may react with other substrates of CYP2B6.[28]
	Certain antidepressants, antipsychotics, beta blockers, type 1C antiarrhythmics, and other CYP2D6 substrates	CYP2D6 metabolism	Although bupropion is not metabolized by CYP2D6, there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by it. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, consider the need to decrease the dose of the original medication, particularly for those concomitant medications with a narrow therapeutic index. [28,30]
	TCAs, systemic steroids, alcohol, nicotine replacement products, abrupt regimen discontinuations, antipsychotics, MAOIs and other CYP2D6 inhibitors	CYP2D6 inhibition or via other mechanisms	Could lower seizure threshold; use low initial dosing and increase dose gradually. Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives (including benzodiazepines) may alter the seizure threshold and is contraindicated in these patients.[28,30]
	Amantadine, levodopa	Unknown	Limited data suggests a higher incidence of adverse experiences (nausea, vomiting, excitation, restlessness, postural tremor) in combination with these medications. When starting bupropion concurrently with these use small initial doses and gradual dose increases.[28,30]

Affected Drug(s)	Affected By	Mechanism	Reasons/Results/Significance
Duloxetine	Cimetidine, fluvoxamine, quinolone antimicrobials, and other CYP1A2 inhibitors	CYP1A2 inhibition	When duloxetine was co-administered with fluvoxamine, a potent CYP1A2 inhibitor, to male subjects (n=14) the AUC was increased over 5-fold, the C_{max} was increased about 2.5-fold, and duloxetine $t_{1/2}$ was increased approximately 3-fold. Other CYP1A2 inhibitors could have similar results.[31]
	TCAs, antipsychotics, cimetidine, and other CYP2D6 inhibitors	CYP2D6 inhibition	Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does result in higher concentrations of duloxetine. [31]
CYP2D6 Substrates	**Duloxetine**	CYP2D6 inhibition	Duloxetine is a moderate inhibitor of CYP2D6 and increases the AUC and C_{max} of drugs metabolized by CYP2D6. Therefore, co-administration of duloxetine with other drugs that are extensively metabolized by this isoenzyme and that have a narrow therapeutic index should be approached with caution.[31]
Highly protein-bound drugs		Drug displacement	Because duloxetine is highly bound to plasma protein, administration of duloxetine to a patient taking another drug that is highly protein-bound may cause increased free concentrations of the other drug, potentially resulting in adverse events.[31]
Mirtazapine	Diazepam	Unknown, additive CNS depression	Concomitant administration of diazepam (15 mg) had a minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects. However, the impairment of motor skills produced by mirtazapine has been shown to be additive with those caused by diazepam.[33]
Clonidine	**Mirtazapine**	Alpha-2 antagonism	A case report describes a patient that experienced a potential interaction between mirtazapine and clonidine that led to hypertensive urgency. [9] The pharmacology of these two drugs supports the explanation for loss of antihypertensive effect.[28]
Venlafaxine	TCAs, antipsychotics, cimetidine and other CYP2D6 inhibitors	CYP2D6 inhibition	Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Therefore, the potential exists for a drug interaction between venlafaxine and drugs that inhibit this isoenzyme.[32]
CYP2D6 Substrates: desipramine, risperidone, indinavir	**Venlafaxine**	CYP2D6 inhibition	In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. These findings have been confirmed in a clinical drug interaction study comparing the effect of venlafaxine with that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.[32]

Affected Drug(s)	Affected By	Mechanism	Reasons/Results/Significance
Haloperidol	**Venlafaxine**	Unknown, possibly CYP2D6[10]	Venlafaxine administered under steady-state conditions at 150 mg/day in 24 healthy subjects decreased total oral-dose clearance (Cl/F) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life ($t_{1/2}$) was unchanged. The mechanism explaining this finding is unknown. Venlafaxine increases haloperidol serum concentrations and thus increases risk of cardiotoxicity (QTc prolongation, Torsades de pointes, cardiac arrest).[28,32]

VI. Adverse Drug Events

The Food and Drug Administration (FDA) requires manufacturers to include a black-box warning notifying prescribers of the potential of antidepressants to increase suicidal thoughts in children and adolescents.[42] In addition, the FDA issued a public health advisory cautioning that adults being treated with antidepressant medications, particularly those being treated for depression, should be watched closely for worsening of depression and for increased suicidal thinking or behavior.

Monoamine Oxidase Inhibitors (MAOIs)[27]

MAOIs cause an increase in endogenous epinephrine, norepinephrine, and serotonin throughout the nervous system leading to significant and common adverse drug events. The most common adverse drug events associated with the MAOIs are orthostatic and postural hypotension, syncope, palpitations, tachycardia, dizziness, headache, hyperreflexia, tremors, muscle twitching, mania, hypomania, confusion, memory impairment, sleep disturbances including hypersomnia and insomnia, weakness, myoclonic movements, fatigue, drowsiness, restlessness, overstimulation including increased anxiety, agitation, manic symptoms, constipation, GI disturbances, nausea, diarrhea, abdominal pain, edema, dry mouth, elevated serum transaminases, weight gain, sexual disturbances, anorexia, blurred vision, impotence, and chills.

Hypertensive crisis can occur when MAOIs are administered concomitantly with foods high in tyramine content or with sympathomimetic medications. Hypertensive crisis is characterized by severe occipital and temporal headache, diaphoresis, mydriasis, elevation of both systolic and diastolic blood pressures, neck stiffness, and neuromuscular excitation. Although rare, cardiac abnormalities, heart failure, or intracerebral hemorrhage can occur.

Paroxetine

The pregnancy subsection of paroxetine products reports preliminary results of a retrospective study suggesting an increased risk of congenital malformations, such as cardiovascular malformations, associated with paroxetine use during the first trimester.

Table 6a. Adverse Events (%) by System for the Selective-serotonin Reuptake Inhibitors [27]

Adverse Event	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Paroxetine CR	Sertraline
Cardiovascular							
Chest pain	–	≥1	≥1	–	3	1	≥1
Hot flushes	0.1-1	≥1	–	–	–	–	0.1-1
Hypertension	0.1-1	≥1	≥1	≥1	≥1	2	0.1-1
Hypotension (postural)	≥1	–	0.1-1	≥1	–	0.1-1	0.1-1
Palpitations	–	≥1	1-3	3	2-3	0.1-1	≥1
Syncope	0.1-1	0.1-1	0.1-1	≥1	≥1	–	0.1-1
Tachycardia	≥1	0.1-1	0.1-1	≥1	≥1	1-2	0.1-1
Vasodilation	–	–	2-3	3	2-4	2-3	< 0.1
Central Nervous System							
Abnormal dreams	–	3	3	–	3-4	1	0.1-1
Abnormal thinking	–	–	2-6	–	0.1-1	0.1-1	–
Agitation	3	0.1-1	≥1	2	3-6	2-3	1-6
Amnesia	≥1	0.1-1	≥1	≥1	2	0.1-1	0.1-1
Anxiety	4	–	12-13	1-5	2-6	2-5	4
Apathy	≥1	0.1-1	–	≥1	–	–	0.1-1
CNS stimulation	–	–	0.1-1	2	–	–	–
Concentration, decreased/impaired	≥1	≥1	–	–	3-4	1-3	–
Confusion	≥1	0.1-1	≥1	–	1	1	0.1-1
Depersonalization	0.1-1	0.1-1	0.1-1	0.1-1	3	0.1-1	–
Depression	≥1	0.1-1	–	2	–	2	0.1-1
Dizziness	–	4-7	2-11	2-11	6-14	6-14	6-17
Drugged feeling	–	–	–	–	2	–	–
Emotional lability	0.1-1	0.1-1	≥1	0.1-1	≥1	0.1-1	0.1-1
Fatigue	5	2-8	–	–	–	–	10-16
Headache	–	24	13-24	3-22	17-18	15-27	25
Hypertonia	0.1-1	–	0.1-1	2	0.1-1	2-3	≥1
Hypoesthesia	0.1-1	–	0.1-1	–	0.1-1	0.1-1	≥1
Hypo-/Hyperkinesia	0.1-1	–	–	≥1	0.1-1	0.1-1	0.1-1
Insomnia	15	7-14	9-24	4-21	11-24	7-20	12-28
Libido decreased	1-4	3-7	3-9	2	3-12	7-12	1-11
Manic reaction	–	–	–	≥1	–	–	–
Myoclonus/twitching	–	0.1-1	0.1-1	≥1	2-3	1-2	0.1-1
Nervousness	–	0.1-1	3-14	2-12	3-9	2-8	5
Paresthesia	≥1	2	–	–	4	1-3	2
Psychotic reaction	–	–	–	≥1	–	–	–
Sleep disorder	–	–	≥1	0.1-1	–	–	–
Somnolence	18	4-13	12-13	4-22	13-24	3-22	2-15
Tremor	8	0.1-1	9-12	5	4-15	4-8	< 1-11
Vertigo	0.1-1	0.1-1	–	0.1-1	≥1	2	0.1-1
Dermatologic							
Acne	0.1-1	0.1-1	0.1-1	0.1-1	0.1-1	0.1-1	0.1-1
Pruritus	≥1	0.1-1	3	–	≥1	0.1-1	0.1-1
Rash	≥1	≥!	4-5	–	2-3	≥1	3

Adverse Event	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Paroxetine CR	Sertraline
Sweating, excessive/increased	11	3-8	7-8	7	1-14	6-14	3-11
Gastrointestinal							
Abdominal pain	3	2	6	1	4	3-7	2-7
Anorexia	4	–	10-11	1-6	–	–	3-11
Constipation	–	3-6	5	10	5-16	2-13	1-8
Decreased appetite	–	3	–	–	2-9	1-12	–
Diarrhea/loose stools	8	6-14	2-11	1-11	9-19	6-18	13-24
Dry mouth	20	4-9	9-11	1-14	9-21	2-18	6-16
Dyspepsia	5	2-6	7-8	1-10	2-5	2-13	6-13
Dysphagia	0.1-1	–	0.1-1	2	0.1-1	–	0.1-1
Flatulence	≥1	2	3	4	4	6-8	–
Gastroenteritis	0.1-1	≥1	0.1-1	0.1-1	0.1-1	0.1-1	0.1-1
Increased appetite	≥1	≥1	≥1	–	2-4	–	≥1
Melena	–	–	0.1-1	–	–	–	< 0.1
Nausea	21	15-18	9-27	9-40	15-36	17-23	13-30
Oropharynx disorder	–	–	–	–	2	–	–
Tooth disorder/caries	–	2	–	3	< 0.1	0.1-1	0.1-1
Vomiting	4	3	1-3	2-5	2-3	2	4
Genitourinary							
Abnormal ejaculation	6	9-14	–	8	6-28	15-27	7-19
Female genital disorders	–	–	–	–	2-9	2-10	–
Male genital disorders, others	–	–	–	–	4-10	–	–
Menstrual disorder	–	2	–	–	–	1-2	0.1-1
Sexual dysfuction/impotence /anorgasmia	1-3	2-6	0.1-1	2	2-13	5-10	≥1
Urinary frequency	–	≥1	2	3	2-3	2	0.1-1
Urinary tract infection	–	≥1	–	0.1-1	2	3	–
Urination disorder/retention	0.1-1	–	0.1-1	1	3	2	0.1-1
Musculoskeletal							
Arthralgia	2	≥1	–	0.1-1	≥1	2	0.1-1
Myalgia	2	≥1	–	–	2-4	5	≥1
Myasthenia	–	–	< 0.1	0.1-1	1	< 0.1	–
Myopathy	–	–	< 0.1	< 0.1	2	< 0.1	–
Respiratory							
Bronchitis	0.1-1	≥1	–	0.1-1	0.1-1	1-2	< 0.1
Cough (increased)	≥1	≥1	–	≥1	≥1	1-2	0.1-1
Dyspnea	0.1-1	–	–	2	0.1-1	–	0.1-1
Pharyngitis	–	–	6-10	–	4	8	-
Respiratory disorder	–	–	–	–	7	–	–
Rhinitis	5	5	16-23	–	3	4	≥1
Sinusitis	3	3	–	≥1	4	4-8	0.1-1

Adverse Event	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Paroxetine CR	Sertraline
Upper respiratory tract infection	5	–	–	9	–	–	0.1-1
Yawn	2	2	3-5	2	2-5	2-5	≥1
Special Senses							
Amblyopia	–	–	–	3	–	–	–
Taste perversion/change	≥1	0.1-1	≥1	3	2	2	–
Tinnitus	0.1-1	≥1	≥1	–	≥1	0.1-1	≥1
Vision disturbances/blurred vision/ abnormal vision	≥1	≥1	2-3	–	2-8	1-5	3
Miscellaneous							
Accidental injury/trauma	–	–	1-8	≥1	3-6	3-8	–
Allergy/allergic reaction	–	≥1	–	0.1-1	0.1-1	2	< 0.1
Asthenia	–	0.1-1	8-14	2-14	3-22	14-18	≥1
Back pain	–	–	–	–	3	4-5	≥1
Chills	–	0.1-1	≥1	2	2	0.1-1	–
Edema	0.1-1	–	–	≥1	0.1-1	0.1-1	0.1-1
Fever	2	≥1	2-5	–	–	0.1-1	0.1-1
Flu syndrome	0.1-1	5	3-12	3	5-6	6-8	–
Malaise	–	0.1-1	0.1-1	≥1	0.1-1	0.1-1	< 1-10
Pain	–	–	3-9			3	1-6
Weight gain	≥1	≥1	≥1	≥1	≥1	1-3	≥1
Weight loss	≥1	0.1-1	2-3	≥1	0.1-1	1	0.1-1

Table 6b. Adverse Events (%) by System for Fluoxetine + Olanzapine [22]

Body System/Adverse Event*	Percentage of Patients Reporting Event		
	Olanzapine and Fluoxetine		Placebo (N=477)
	Bipolar depression (N=86)	Various diagnoses (N=571)	
Body as a Whole			
Asthenia	13	15	3
Accidental injury	5	3	2
Fever	4	3	1
Cardiovascular System			
Hypertension	2	2	1
Tachycardia	2	2	0
Digestive System			
Diarrhea	19	8	7
Dry mouth	16	11	6
Increased appetite	13	16	4
Tooth disorder	1	2	1
Metabolic and Nutritional Disorders			
Weight gain	17	21	3
Peripheral edema	4	8	1
Edema	0	5	0
Musculoskeletal System			
Joint disorder	1	2	1
Twitching	6	2	1
Arthralgia	5	3	1
Nervous System			
Somnolence	21	22	11
Tremor	9	8	3
Thinking abnormal	6	6	3
Libido decreased	4	2	1
Hyperkinesia	2	1	1
Personality disorder	2	1	1
Sleep disorder	2	1	1
Amnesia	1	3	0
Respiratory System			
Pharyngitis	4	6	3
Dyspnea	1	2	1
Special Senses			
Amblyopia	5	4	2
Ear pain	2	1	1
Otitis media	2	0	0
Speech disorder	0	2	0
Urogenital System			
Abnormal ejaculation^	7	2	1
Impotence	4	2	1
Anorgasmia	3	1	0

* Included are events reported by at least 2% of patients taking olanzapine and fluoxetine except the following events, which had an incidence of placebo > SYMBYAX: abdominal pain, abnormal dreams, agitation, akathisia, anorexia, anxiety, apathy, back pain, chest pain, constipation, cough increased, depression, dizziness, dysmenorrhea, dyspepsia, flatulence, flu syndrome, headache, hypertonia, insomnia, manic reaction, myalgia, nausea, nervousness, pain, palpitation, paresthesia, rash rhinitis, sinusitis, sweating, vomiting.
^ Adjusted for gender.

Nefazodone[27]

Approximately 16% of the 3,496 patients who received nefazodone in worldwide post marketing clinical trials discontinued treatment because of an adverse experience. The most common adverse events in clinical trials associated with discontinuation of nefazodone included: nausea (3.5%), dizziness (1.9%), insomnia (1.5%), asthenia (1.3%), and agitation (1.2%).

Nefazodone carries a "black box warning" due to reports of life-threatening hepatic failure. The reported rate in the US is approximately 1 case of liver failure resulting in death or transplant per 250,000 to 300,000 patient-years of nefazodone treatment.

Table 6c. Nefazodone Adverse Reactions[27]

Adverse Reaction	Nefazodone (n=393)	Placebo (n=394)
Cardiovascular		
Postural hypotension	4%	1%
Hypotension	2%	1%
CNS		
Somnolence	25%	14%
Dizziness	17%	5%
Insomnia	11%	9%
Lightheadedness	10%	3%
Confusion	7%	2%
Memory impairment	4%	2%
Paresthesia	4%	2%
Vasodilation (eg, flushing, feeling	4%	2%
warm)	3%	2%
Abnormal dreams	3%	1%
Concentration decreased	2%	0%
Ataxia	2%	1%
Incoordination	2%	1%
Psychomotor retardation	2%	1%
Tremor	1%	0%
Hypertonia	1%	<1%
Libido decreased		
Dermatological		
Pruritis	2%	1%
Rash	2%	1%
GI		
Dry mouth	25%	13%
Nausea	22%	12%
Constipation	14%	8%
Dyspepsia	9%	7%
Diarrhea	8%	7%
Increased appetite	5%	3%
Nausea and vomiting	2%	1%
GU		
Urinary frequency	2%	1%
Urinary tract infection	2%	1%
Urinary retention	2%	1%
Vaginitis	2%	1%
Breast pain	1%	<1%
Metabolic		
Peripheral edema	3%	2%
Thirst	1%	<1%
Respiratory		
Pharyngitis	6%	5%

Adverse Reaction	Nefazodone (n=393)	Placebo (n=394)
Cough increased	3%	1%
Special senses		
Blurred vision	9%	3%
Abnormal vision	7%	1%
Tinnitus	2%	1%
Taste perversion	2%	1%
Visual field defect	2%	0%
Miscellaneous		
Headache	36%	33%
Asthenia	11%	5%
Infection	8%	6%
Flu syndrome	3%	2%
Chills	2%	1%
Fever/neck rigidity	2%	1%
Arthralgia	1%	0%
	1%	<1%

Trazodone

Priapism has been reported in patients taking trazodone. This side effect is rare but dangerous, and occurs in approximately 1 in 10,000 patients.[40]

Trazodone is not recommended during the initial recovery phase of MI and should be used with caution in patients with cardiac disease since trazodone has rarely been associated with cardiac arrhythmias.[27]

Table 6d. Trazodone Adverse Reactions (%)[27]

	Inpatients		Outpatients	
Adverse reaction	Trazodone (n=142)	Placebo (n=95)	Trazodone (n=157)	Placebo (n=158)
Cardiovascular				
Hypertension	2.1	1.1	1.3	<1
Hypotension	7	1.1	3.8	0
Shortness of breath	<1	1.1	1.3	0
Syncope	2.8	2.1	4.5	1.3
Tachycardia/palpitations	0	0	7	7
CNS				
Anger/hostility	3.5	6.3	1.3	2.5
Confusion	4.9	0	5.7	7.6
Decreased concentration	2.8	2.1	1.3	0
Disorientation	2.1	0	<1	0
Dizziness/lightheadedness	19.7	5.3	28	15.2
Drowsiness	23.9	6.3	40.8	19.6
Excitement	1.4	1.1	5.1	5.7
Fatigue	11.3	4.2	5.7	2.5
Headache	9.9	5.3	19.8	15.8
Incoordination	1.9	0	1.9	0
Insomnia	9.9	10.5	6.4	12
Impaired memory	1.4	0	<1	<1
Nervousness	14.8	10.5	6.4	8.2
Nightmares/vivid dreams	<1	1.1	5.1	5.7
Paresthesia	1.4	0	0	<1
Tremors	2.8	1.1	5.1	3.8
GI				
Abdominal/gastric disorder	3.5	4.2	5.7	4.4
Bad taste in mouth	1.4	0	0	0

Adverse reaction	Inpatients		Outpatients	
	Trazodone (n=142)	Placebo (n=95)	Trazodone (n=157)	Placebo (n=158)
Constipation	7	4.2	7.6	5.7
Diarrhea	0	1.1	4.5	1.9
Dry mouth	14.8	8.4	33.8	20.3
Nausea/vomiting	9.9	1.1	12.7	9.5
Special senses				
Blurred vision	6.3	4.2	14.7	3.8
Eyes red/tired/itching	2.8	0	0	0
Tinnitus	1.4	0	0	<1
Miscellaneous				
Allergic skin condition	2.8	1.1	7	1.3
Aches/pains	5.6	3.2	5.1	2.5
Decreased appetite	3.5	5.3	0	<1
Decreased libido	<1	1.1	1.3	<1
Head full/heavy	2.8	0	0	0
Malaise	2.8	0	0	0
Nasal/sinus congestion	2.8	0	5.7	3.2
Sweating/clamminess	1.4	1.1	<1	<1
Weight gain	1.4	0	4.5	1.9
Weight loss	<1	3.2	5.7	2.5

Tricyclic Antidepressants and Other Norepinephrine-reuptake Inhibitors

These medications have a narrow therapeutic index and can be fatal with as little as a week's medication.[35] Toxicity in overdose is due to central nervous system toxicity as well as quinidine-like effects (Na channel blockade).[36] Photosensitization (photoallergy or phototoxicity) may occur; therefore, patients should take protective measures (e.g., sunscreens, protective clothing) against exposure to ultraviolet light or sunlight until tolerance is determined.[27]

Table 6e. Adverse Events for the Tricyclic Antidepressants and Other Norepinephrine-reuptake Inhibitors[43]

Drug	Reuptake Antagonism		Anti-cholinergic Effects	Histamine-1 Antagonism	Alpha-1 Antagonism	Seizures	Conduction Abnormalities
	Norepinephrine	Serotonin					
Tricyclic Antidepressants							
Tertiary amines							
Amitriptyline	++	++++	++++	++++	+++	+++	+++
Clomipramine	++	+++	++++	++++	++	++++	+++
Doxepin	++	++	+++	++++	++	+++	++
Imipramine	+++	+++	+++	+++	++++	+++	+++
Trimipramine	++	++	++++	++++	+++	+++	+++
Secondary amines							
Desipramine	++++	+	++	++	++	++	++
Nortriptyline	+++	++	++	++	+	++	++
Protriptyline	+++	++	++	+	++	++	+++
Dibenzoxazepine							
Amoxapine	+++	++	+++	++	++	+++	++
Tetracyclics							
Maprotiline	+++	+	+++	+++	++	++++	++

Anticholinergic effects result in dry mouth, constipation, blurred vision, memory and other cognitive impairments, and minor sedation.
Histamine-1 antagonism results in sedation and minor weight gain.
Alpha-1 antagonism results in orthostasis.

Table 6f. Adverse Events (%) for the Miscellaneous Antidepressants[28, 32]

	Bupropion	Duloxetine	Mirtazapine	Venlafaxine
Cardiovascular				
Cardiac dysrhythmias	<1%			
Hypertension	1-5%			1-5%
Tachyarrythmias	1-5%			
Vasodilation				1-5%
Dermatologic				
Excessive sweating	5-10%	5-10%		10-20%
Pruritus	1-5%			
Rash	1-5%			
Endocrine/Metabolic				
Decreased appetite		5-10%		10-20%
Increased appetite			10-20%	
Increased serum cholesterol			5-10%	
Increased serum triglycerides			5-10%	
Weight gain			5-10%	
Weight loss				1-5%
Gastrointestinal				
Aptyalism	5-10%	10-20%		
Constipation	5-10%	10-20%	5-10%	5-10%
Diarrhea		5-10%		1-5%
Flatulence				1-5%
Gastritis		5-10%		
Nausea	1-5%	10-20%		30-40%
Vomiting	1-5%			1-5%
Hematologic				
Agranulocytosis			<1%	
Neutropenia			<1%	
Hepatic/Renal				
Increased ALT			1-5%	
Hepatitis				<1%
Dysuria		5-10%		
Neurologic				
Abnormal vision	1-5%	5-10%		1-5%
Asthenia			1-5%	10-20%
Confusion	1-5%			
Dizziness	5-10%	5-10%	1-5%	10-20%
Dry mouth				10-20%
Headache	1-5%			10-20%
Insomnia	1-5%	10-20%		10-20%
Nervousness	1-5%			5-10%
Seizures	<1%			
Somnolence		5-10%	30-40%	10-20%
Tremor	10-20%			1-5%
Psychiatric				
Abnormal dreams			1-5%	1-5%
Agitation	5-10%			1-5%
Depression, worsening	<1%	<1%	<1%	<1%
Suicidal thoughts/suicide	<1%	<1%	<1%	<1%
Reproduction				
Abnormal ejaculation		1-5%		10-20%
Decreased libido		1-5%		5-10%
Impotence	<1%	1-5%	<1%	5-10%

VII. Dosing and Administration

Table 7a. Dosing for the Monoamine Oxidase Inhibitors[15-17]

Generic Name	Formulations	Dose/Frequency/Duration
Isocarboxazid	10mg oral tablets	Initial dose: 10mg twice daily Maximum dose: 60mg daily
Phenelzine	15mg oral tablets	Initial dose: 15mg three times daily Maximum dose: 90mg daily
Tranylcypromine	10mg oral tablets	Initial dose: 30mg daily Maximum dose: 60mg daily

Table7b. Dosing and Administration for the Selective-serotonin Reuptake Inhibitors[18,26]

Generic Name	Formulations	Dose/Frequency/Duration
Citalopram	10 mg oral tablets 20 mg oral tablets 40 mg oral tablets 10 mg/5 ml oral solution	<u>Depression</u> Initial: 20 mg/day in AM or PM Maximum: 60 mg/day
Escitalopram	5 mg oral tablet 10 mg oral tablet 20 mg oral tablet 5 mg/5 ml oral solution	<u>Depression, GAD</u> Initial: 10 mg/day in AM or PM Maximum: 20 mg/day
Fluoxetine	10 mg oral capsules 20 mg oral capsules 40 mg oral capsules 20 mg/5 ml oral solution 10 mg oral tablets 20 mg oral tablets	<u>Depression, OCD, PMDD, bulimia</u> Initial: 20 mg/day in AM. Maximum: 80 mg/day (depression, OCD); doses not studied above 60 mg/d (bulimia) <u>Panic disorder</u> Initial: 10 mg/day Maximum: doses not studied above 60 mg/d <u>PMDD</u> Initial: 20 mg/day continuously or 20 mg/day starting 14 days prior to menstruation and through first full day of menses (repeat with each cycle) Maximum: doses not studied above 60 mg/d
	90 mg oral delayed release capsules	Initiate 7 days after last daily dose of fluoxetine 20mg/day
Fluoxetine and olanzapine	25 mg fluoxetine + 6 mg Olanzapine oral capsules 25 mg fluoxetine + 12 mg Olanzapine oral capsules 50 mg fluoxetine + 6 mg Olanzapine oral capsules 50 mg fluoxetine + 12 mg Olanzapine oral capsules	Initial: olanzapine 6 mg/fluoxetine 25 mg/day in PM Maximum: safety of daily doses of olanzapine >18 mg/fluoxetine >75 mg have not been evaluated
Fluvoxamine	25 mg oral tablets 50 mg oral tablets 100 mg oral tablets	Initial: 50 mg at bedtime Usual dose range: 100-300 mg/day: doses > 100 mg/day should be divided into 2 doses

Generic Name	Formulations	Dose/Frequency/Duration
Paroxetine HCL	10 mg oral tablets 20 mg oral tablets 30 mg oral tablets 40 mg oral tablets 10 mg/5 ml oral suspension	Depression Initial: 20 mg/day in AM Maximum dose: 50 mg/day GAD Initial: 20 mg/day in AM Maximum: no greater benefit was seen with doses >20 mg OCD Initial: 20 mg/day in AM. Maximum dose: 60 mg/day Panic disorder: Initial: 10 mg/day in AM Maximum dose: 60 mg/day PMDD Initial: 12.5 mg/day in AM. Maximum: 25 mg/day. May be given daily throughout the menstrual cycle or limited to the luteal phase. PTSD Initial: 20 mg/day SAD: Initial: 20 mg/day Maximum: doses >20 mg/day may not have additional benefit
	12.5 mg oral tablets 25 mg oral tablets 37.5 mg oral tablets	Depression Initial: 25 mg/day Maximum: 62.5 mg/day Panic disorder Initial: 12.5 mg/day Maximum: 75 mg/day PMDD Initial: 12.5 mg/day in AM. Maximum: 25 mg/day. May be given daily throughout the menstrual cycle. Social anxiety disorder Initial: 12.5 mg/day in AM Maximum dose: 37.5 mg/day Menopause-associated vasomotor symptoms[§] 12.5-25 mg/day

Generic Name	Formulations	Dose/Frequency/Duration
Paroxetine mesylate	10 mg oral tablets 20 mg oral tablets 30 mg oral tablets 40 mg oral tablets	Depression Initial: 20 mg/day Maximum: 50 mg/day OCD Initial: 20 mg/day Maximum: 60 mg/day Panic disorder Initial: 10 mg/day Maximum: 60 mg/day
Sertraline	25 mg oral tablets 50 mg oral tablets 100 mg oral tablets 20 mg/ml oral concentrate solution	Depression/OCD Initial: 50 mg/day. Increase at 1 week intervals Maximum: 200 mg/day . Panic disorder, PTSD, social anxiety disorder Initial: 25 mg/day Maximum:50 mg/day Premenstrual dysphoric disorder (PMDD) Initial: 50 mg/day either daily throughout menstrual cycle or limited to the luteal phase Maximum: 150 mg/day when dosing throughout menstrual cycle or up to 100 mg day when dosing during luteal phase only. If a 100 mg/day dose has been established with luteal phase dosing, a 50 mg/day titration step for 3 days should be utilized at the beginning of each luteal phase dosing period.

Table 7c. Dosing for the Serotonin Modulators for Depression[28,29]

Generic Name	Availability	Dose/Frequency/Duration
Nefazodone	50, 100, 150, 200, and 250 mg oral tablets	Initial dose: 200 mg/day, in 2 divided doses Usual effective dosage range: 300-600 mg/day
Trazodone	50, 100, 150, and 300 mg oral tablets	Initial dose: 150 mg/day, in divided doses Maximum dose (outpatient): 400 mg/day Maximum dose (inpatient): 600 mg/day

Tricyclics and Other Norepinephrine-reuptake Inhibitors

The goal of treatment is to reach a therapeutic effect using the lowest possible dose. Like other antidepressant agents, the optimal effect usually takes 4-8 weeks to occur. Therefore, it is important to give these agents a proper trial. Monotherapy is preferred for Major Depressive Disorder (MDD). However, combination therapy may sometimes be necessary. Amitriptyline is approved for children 12 and older. However, the FDA has mandated that the pediatric patient be closely monitored for suicidality. Table 7d summarizes the manufacturers' proposed dosing regimens for each medication.

Table 7d. Dosing and Administration for the Tricyclics and Other Norepinephrine-reuptake Inhibitors[27]

Generic Name	Usual Adult Dose	Adolescent/Elderly/Pediatric Doses	Availability
Amitriptyline	• Outpatient: 75 mg/day in divided doses, may gradually increase to 150 mg/day. Alternatively, initiate therapy with 50 to 100 mg at bedtime. Increase by 25 to 50 mg as necessary, to a total of 150 mg/day. • Maintenance: 40 to 100 mg/day. When patient has satisfactorily improved, reduce dosage to the lowest effective amount.	• 10 mg 3 times/day with 20 mg at bedtime may be satisfactory in adolescent and elderly patients who cannot tolerate higher dosages. • Not recommended for children younger than 12 years of age.	Tablet: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg Vial: 10 mg/ml
Amitriptyline + chlordiazepoxide	• Initially, administer chlordiazepoxide 10 mg with 25 mg 3 or 4 times daily in divided doses; increase to 6 times daily, as required. Some patients respond to smaller doses and can be maintained on 2 tablets daily. After a satisfactory response is obtained, reduce dosage to smallest amount needed.	• In general, lower dosages are recommended for elderly patients.	Tablet: 12.5-5 mg, 25-10 mg
Amitriptyline + perphenazine	• Initially, perphenazine 2 to 4 mg with amitriptyline 10 to 50 mg, 3 or 4 times daily. After a satisfactory response is noted, reduce to smallest amount necessary to obtain relief.	• Not recommended for use in children.	Tablet: 10-2 mg, 10-4 mg, 25-2 mg, 25-4 mg, 50-4 mg
Amoxapine	• Initial: 50 mg 2-3 times daily; depending upon tolerance, increase dosage to 100 mg 2 or 3 times daily by the end of the first week. Increase above 300 mg/day only if 300 mg/day ineffective. • Maintenance: once an effective dosage is established, the drug may be given in a single bedtime dose (not to exceed 300 mg). If the total daily dosage exceeds 300 mg, give in divided doses.	• Initial dose elderly: 25 mg 2 or 3 times/day. If tolerated, dosage may be increased by the end of the first week to 50 mg 2 or 3 times/day. If 100 to 150 mg/day not adequate, increase dose, up to maximum of 300 mg/day. • Maintenance dose elderly: Once an effective dosage is established, give amoxapine in a single bedtime dose, not to exceed 300 mg.	Tablet: 25 mg, 50 mg, 100 mg, 150 mg

Generic Name	Usual Adult Dose	Adolescent/Elderly/Pediatric Doses	Availability
Clomipramine	• Initial: 25 mg daily, gradually increase, as tolerated, to approximately 100 mg during the first 2 weeks. Administer in divided doses with meals to reduce GI side effects. • Maintenance: may be increased gradually over the next several weeks to a maximum of 250 mg/day.	• Children and adolescents: Initiate at 25 mg daily and gradually increase during the first 2 weeks, as tolerated, to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Administer in divided doses with meals to reduce GI side effects. • Children and adolescents: May be increased to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller.	Capsule: 25 mg, 50 mg, 75 mg Tablet: 100 mg
Desipramine	• 100 to 200 mg/day. Gradually increase to 300 mg/day maximum dose if necessary.	• 25 to 100 mg/day. Can be given in divided doses or as a single daily dose. Dosages greater than 150 mg/day not recommended.	Tablet: 10 mg, 25 mg, 50 mg, 75 mg, 150 mg
Doxepin	• Mild to moderate illness: initially, 75 mg/day, usual optimum dosage is 75 to 150 mg/day (maximum dose). • Mild symptomatology or emotional symptoms accompanying organic disease: 25 to 50 mg/day is often effective. • More severe anxiety or depression: higher doses (eg, 50 mg 3 times/day) may be required; if necessary, gradually increase to 300 mg/day. Additional effectiveness is rarely obtained by exceeding 300 mg/day.	• Not recommended for use in children younger than 12 years of age.	Capsule: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg Oral concentrate: 10 mg/ml
Imipramine HCl	• Hospitalized patients: initially, 100 mg/day orally in divided doses; gradually increase to 200 mg/day, as required. If no response occurs after 2 weeks, increase to 250 to 300 mg/day once daily. • Outpatients: initially, 75 mg/day, increased to 150 mg/day. Do not exceed 200 mg/day. • Maintenance: 50 to 150 mg/day or lowest dose that will maintain remission.	• Initially, 30 to 40 mg/day orally; generally not necessary to exceed 100 mg/day.	Tablet: 10 mg, 25 mg, 50 mg

Generic Name	Usual Adult Dose	Adolescent/Elderly/Pediatric Doses	Availability
Imipramine pamoate	• Hospitalized patients: initiate therapy at 100 to 150 mg/day; may be increased to 200 mg/day. If there is no response after 2 weeks, increase dosage to 250 to 300 mg/day. • Outpatients: initiate therapy at 75 mg/day. Dosage may be increased to 150 mg/day, which is the dose level at which optimum response is usually obtained. If necessary, dosage may be increased to 200 mg/day. In some patients it may be necessary to employ a divided-dose schedule. • Maintenance: maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission after which the dosage should gradually be decreased. The usual maintenance dose is 75 to 150 mg/day. In some patients it may be necessary to employ a divided-dose schedule.	• Initial: 25 to 50 mg daily with imipramine HCl because imipramine pamoate does not come in those strengths. Dosage may be increased according to response and tolerance, but it is generally unnecessary to exceed 100 mg/day in these patients. Imipramine pamoate capsules may be used when total daily dosage is established at 75 mg or more.	Capsule: 75 mg, 100 mg, 125 mg, 150 mg
Maprotiline	• Initial: 75 mg/day for outpatients with mild to moderate depression. In some patients, especially the elderly, an initial dosage of 25 mg/day may be used. Maintain the initial dosage for 2 weeks. The dose may then be increased gradually in 25 mg increments, as required and tolerated. A maximum daily dose of 150 mg/day will result in therapeutic efficacy in most outpatients, but dosages as high as 225 mg/day may be required. • Severe depression: for hospitalized patients, an initial daily dose of 100 to 150 mg which may be gradually increased as required and tolerated, up to a maximum of 225 mg/day. • Maintenance: keep at the lowest effective level; may be reduced to 75 to 150 mg/day with adjustment depending on therapeutic response.	• An initial dosage of 25 mg/day may be used. • In general, lower doses are recommended; 50 to 75 mg/day satisfactory as maintenance therapy for elderly patients who do not tolerate higher amounts.	Tablet: 25 mg, 50 mg, 75 mg

Generic Name	Usual Adult Dose	Adolescent/Elderly/Pediatric Doses	Availability
Nortriptyline	• 25 mg 3 or 4 times daily; begin at a low level and increase as required. The total daily dose can be given at bedtime. Optimum plasma levels of 50 to 150 ng/mL should be maintained at doses greater than 100 mg/day. Doses greater than 150 mg/day are not recommended.	• 30 to 50 mg daily in divided doses or total daily dose may be given once/day.	Capsule: 10 mg, 25 mg, 50 mg, 75 mg Solution: 10 mg/5ml
Protriptyline	• 15 to 40 mg/day divided into 3 or 4 doses. May increase to 60 mg/day (maximum dose). When satisfactory improvement has been reached, reduce dosage to the smallest amount that will maintain relief of symptoms.	• 15 to 40 mg/day divided into 3 or 4 doses. May increase to 60 mg/day (maximum dose). When satisfactory improvement has been reached, reduce dosage to the smallest amount that will maintain relief of symptoms.	Tablet: 5 mg, 10 mg
Trimipramine	• Hospitalized patients: initially, 100 mg/day twice daily, increase gradually to 200 mg/day depending upon individual response and tolerance. If improvement does not occur in 2 to 3 weeks, increase to a maximum dose of 250 to 300 mg/day. • Outpatients: initially, 75 mg/day in divided doses; increase to 150 mg/day. Do not exceed 200 mg/day. The total dosage requirement may be given at bedtime.	• Initially, 50 mg/day, with gradual increments up to 100 mg/day.	Capsule: 25 mg, 50 mg, 100 mg

Special Dosing Considerations

Renal Impairment

Since these medications are principally metabolized via the liver, changes in renal function do not necessarily require a dose change. However, there is a potential accumulation of metabolites which confer little beneficial effect but may lead to toxicity. In the case of nortriptyline this could lead to the increase in the 10-hydroxy-nortriptyline metabolite while the parent drug serum levels stay the same. Caution is warranted when treating patients with renal failure with these agents. Conversion to another class may be necessary.[35,38]

Hepatic Impairment

Patients with hepatic impairment may require a lowering of the dose but the manufacturers recommend that one monitor for emergence of side effects and adjust accordingly.

Geriatric Patients

Use of these antidepressants in the geriatric population is considered a relative contraindication.[4] Although the medications are effective for this group, the adverse effect profile limits it use.[44] Antidepressants such as the SSRIs are the preferred agents for this group of patients. Metabolism of some of these medications is not greatly impacted by age and dose adjustments are generally not needed to attain specific serum concentrations.[37]However, tolerability to the adverse effects of this class decreases thus limiting the practicality of these medications.

Pregnancy/Breastfeeding[27]

The following pregnancy classifications apply to the antidepressants included in this review:

Category B: doxepin (cream only), maprotiline
Category C: amitriptyline, amoxapine, clomipramine, desipramine, doxepin (all other forms), protriptyline, trimipramine
Category D: imipramine, nortriptyline

Table7e. Dosage and Administration for the Miscellaneous Antidepressants[28,30-34^]

Generic Name	Availability	Dosing Regimen/Considerations
Bupropion		
Bupropion	75, 100 mg tablets	Food – May be given without regard to meals. Initial – 100 mg BID (200 mg total) as a morning and evening dose. After day 4 – dose may be increased to 100 mg TID (300mg total). Maximum – 450 mg total (in 3-4 divided doses) may be considered after failing several weeks of therapy. There should be a 4 hour interval between doses. Over 450 mg of bupropion daily leads to a fourfold increase in seizure risk.
Bupropion sustained-release	100, 150, 200 mg sustained release tablets	Food – May be given without regard to meals. Initial – 150 mg as a single dose in the morning. After day 4 – If tolerated, a dose of 150 mg BID (300mg total) may be prescribed as one in the morning and one in the evening. Maximum – 400 mg/day (200 mg BID) may be considered in patients who do not respond to several weeks of therapy.
Bupropion extended-release	150, 300 mg extended release tablets	Food– May be given without regard to meals. Initial – 150 mg as a single dose in the morning. After day 4 – If tolerated, a dose of 300 mg may be given as a single dose in the morning. Maximum – 450 mg/day given as a single dose in the morning may be considered in patients who do not respond to several weeks of therapy.
Duloxetine		
Duloxetine	20, 30, 60 mg enteric coated capsules	Food – May be given without regard to meals. Dosing – 40-60 mg daily, either given as 20mg bid, 30mg bid, or 60mg once a day.
Mirtazapine		
Mirtazapine	15, 30, 45 mg tablets 15, 30, 45 mg orally disintegrating tablets	Food – May be given without regard to meals. Initial - 15 mg/day at bedtime. Maximum - may increase dose every 1-2 weeks to a max dose of 45 mg/day.

Generic Name	Availability	Dosing Regimen/Considerations
Venlafaxine		
Venlafaxine	25, 37.5, 50, 75, 100 mg tablets	Food – Should be taken with food. Initial – 75 mg/day in 2-3 divided doses. 4 day intervals – Dose may be increased in units of 75 mg/day. Maximum – 225 mg/day for outpatients.
Venlafaxine extended-release	37.5, 75, 150 mg sustained release capsules	Food – Should be taken with food. Initial – 37.5 – 75 mg/day in a single dose. 4 day intervals – Dose may be increased in units of 75 mg/day. Maximum – 225 mg/day for outpatients.

^The medications in this drug class have not been approved for use in the pediatric population.

Renal Impairment

Bupropion
The manufacturer states that no studies have been done in individuals with renal impairment. To avoid the possibility of accumulation of bupropion and its metabolites in renally impaired patients, the dosing frequency should be reduced and patients should be closely monitored for toxic effects.[30]

Duloxetine
In renally impaired patients, duloxetine should be initiated at a lower dose and then increased gradually. Duloxetine is not recommended for patients with end-stage renal disease (requiring dialysis) or severe renal impairment due to increased plasma concentrations of duloxetine and its metabolites.[31]

Mirtazapine
Elimination of mirtazapine is correlated with creatinine clearance. Total body clearance of mirtazapine was reduced approximately 30% in patients with moderate (Cl_{cr} = 11–39 mL/min/1.73 m^2) and approximately 50% in patients with severe (Cl_{cr} = < 10 mL/min/1.73 m^2) renal impairment when compared to normal subjects. Caution is indicated in administering mirtazapine to patients with compromised renal function.[33]

Venlafaxine
The manufacturer recommends a 25% to 50% decrease in the venlafaxine dose in patients with a creatinine clearance between 10 and 70 milliliters/minute. The dose should be reduced by 50% in patients undergoing hemodialysis; the dose should be administered after the dialysis treatment.[32]

Hepatic Impairment

Bupropion
Bupropion should be used with extreme caution in patients with severe hepatic cirrhosis due to accumulation of the active metabolites of bupropion. A dose not exceeding 75 milligrams daily should be used. [30] Bupropion sustained release should also be used with extreme caution in patients with severe hepatic cirrhosis. The dose used to treat depression in these patients should not exceed 100 mg daily or 150 mg every other day. [30] Bupropion extended release should be used with extreme caution in patients with severe hepatic cirrhosis. The dose used to treat depression in these patients should not exceed 150 mg every other day. [30]

Duloxetine
Duloxetine is not recommended for use in patients with any hepatic insufficiency.[31]

Mirtazapine
Following a single 15 mg oral dose of mirtazapine, the oral clearance of mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering mirtazapine to patients with compromised hepatic function.[33]

Venlafaxine
Venlafaxine clearance is decreased by approximately 30 to 35% in patients with hepatic impairment.[11,12] Total daily dose should be reduced by 50% in patients with moderate hepatic impairment. Further individualization of dose may be necessary in some patients due to the large individual variability in clearance found in this population. [32]

Geriatric Patients

Bupropion
No overall difference in safety or effectiveness has been seen in older patients versus younger patients, and disposition of bupropion and its metabolites appears to be similar. [30]

Duloxetine
No dose adjustment is recommended for elderly patients on the basis of age, but use caution.[31]

Mirtazapine
The clearance of mirtazapine is reduced in elderly patients. Mirtazapine clearance is more drastically decreased in elderly males than in elderly females. Mirtazapine clearance is reduced by 40% in elderly males compared to younger males, while clearance is reduced by 10% in elderly females compared to younger females. Mirtazapine should be administered with caution to elderly patients.[28]

Venlafaxine
Clearance of venlafaxine is reduced by approximately 15% in the elderly, presumably because of the slight decrease in renal function in this age group.[45,46] Dosage adjustment based upon age or gender of the patient is generally unnecessary. [32]

Pregnancy/Breastfeeding

Bupropion
Pregnancy category B for all trimesters.
Thomson Lactation Rating: Infant risk cannot be ruled out. Bupropion and its metabolites are excreted into human breast milk. The potential for adverse effects in the nursing infant from exposure to the drug are unknown; therefore, caution should be exercised with its use in nursing women.[30]

Duloxetine
Pregnancy category C for all trimesters.
Thomson Lactation Rating: Infant risk cannot be ruled out. No reports describing the use of duloxetine during human lactation are available, and the effects on the nursing infant from exposure to the drug in milk are unknown. Breastfeeding while taking duloxetine is not recommended.[33]

Mirtazapine
Pregnancy category C for all trimesters.
Thomson Lactation Rating: Infant risk cannot be ruled out. It is not known if mirtazapine is excreted in human milk. Until more data are available, use caution when considering the use of mirtazapine in lactating women.[33]

Venlafaxine
Pregnancy category C for all trimesters.
Thomson Lactation Rating: Infant risk is minimal. Venlafaxine is excreted in human breast milk in very low concentrations. Drug-related adverse effects in the nursing infants have not been reported. [32]

VIII. Effectiveness

Although the MAOIs have been used in clinical practice for many years, there are limited head-to-head trials comparing these agents. A 1995 review of the MAOIs reported that only 5 randomized controlled trials have directly compared the MAOIs. The authors felt that 2 of the trials were small and results were inconclusive due to the size of the study. They reported that one trial found comparable response rates between tranylcypromine and isocarboxazid, another trial found a trend favoring phenelzine over isocarboxazid, and another study found no difference between phenelzine and isocarboxazid. The authors concluded that firm conclusions about the relative efficacy of the approved MAOIs could not be made.[48]

The efficacy of the TCAs has been demonstrated in numerous placebo-controlled trials and is comparable to the efficacy of the SSRIs.[4,60-62,68] Burke reviewed the literature regarding the outcomes of antidepressants that affect 5-HT only or that have dual neurotransmitter effects of 5-HT and NE.[69] He concluded that head-to-head trials and pooled analyses suggest comparable efficacy between the classes of antidepressants.

Table 8. Outcomes Evidence for the Antidepressants

Study	Methods	Efficacy variables	Results
Tranylcypromine vs. phenelzine[47]	Randomized, double-blind N=77 5 weeks	Hamilton Rating Scale for Depression (HAM-D)	Seventeen (44%) of 39 patients responded to tranylcypromine and 18 (47%) of 38 patients responded to phenelzine (≥ 50% reduction in HAM-D). The mean reduction in HAM-D score was 10.4 ±8.3 for the tranylcypromine sample versus 8.3±8.4 for the phenelzine-treated patients. No significant differences in response between both drugs were observed. A substantial number of patients experienced severe side effects, mainly dizziness, agitation, and insomnia. The incidence was the same in both samples (21%).
Isocarboxazid vs. placebo[15]	Placebo-controlled N=29 N=25 Two 6-week trials	HAM-D Total Score and Depressed Mood Score	The effectiveness of isocarboxazid was established in two 6-week placebo-controlled studies conducted in depressed outpatients with major depressive disorder. In both studies, at the end of 6 weeks, patients receiving isocarboxazid had significantly greater reduction in signs and symptoms of depression evaluated by the HAM-D, for both the Total Score and the Depressed Mood Score than patients who received placebo.
Fluoxetine 20 mg/d versus sertraline 50 mg/d versus	Randomized, double-blind,	Improvement in depression (HAM-	Depression improvement was similar in all patients (p=0.365)

Study	Methods	Efficacy variables	Results
paroxetine 20 mg/d in depression[49]	multi-center study N = 284 10-16 weeks	D-17 scores) Improvement in insomnia (HAM-D sleep disturbance factor score)	 Insomnia improvement was similar in all patients (p=0.868)
Paroxetine (10-40 mg) versus sertraline (25-100 mg) in generalized anxiety disorder[50]	Randomized, double blind, parallel-group, flexible-dose study N = 53 8 weeks	HAM-A, CGI-S (response and remission rates)	Both paroxetine and sertraline resulted in significant reduction in HAM-A scores from baseline (p<0.001) but no significant group effect. HAM-A (paroxetine) = 57% +/- 28% HAM-A (sertraline) = 56% +/- 28% Response (paroxetine) = 68% Response (sertraline) = 61% Remission (paroxetine) = 40% Remission (sertraline) = 46%
Sertraline 50-150 mg/d versus paroxetine 40-60 mg/d in panic disorder[51]	Randomized, double-blind, parallel-group, multi-center study N = 225 12 weeks	Clinician-rated PAS	No significant difference in the PAS scores between the two treatment groups across the agoraphobia and non-agoraphobia subtypes (p=0.487)
Paroxetine 10 mg/d versus 20 mg/d versus 40 mg/d in panic disorder[52]	Randomized, double blind, parallel-group, fixed-dose, placebo-controlled study N = 278 10 weeks	% subjects free of panic attacks Mean change from baseline in number of full panic attacks % subjects with a 50% reduction from baseline in number of full panic attacks CGI-S	% subjects free of panic attacks were 40 mg = 86%, 20 mg = 65.2%, and 10 mg = 67.4% (p<0.019 at weeks 4 and 10) No significant differences between groups in mean change from baseline in number of full panic attacks. No significant differences between groups in % subjects with a 50% reduction from baseline in number of full panic attacks. CGI-S: 40 mg = 81.2% 20 mg = 75.4% 10 mg = 57.8% placebo = 51.5% (significantly higher with 40 and 20 mg p<0.019)

Study	Methods	Efficacy variables	Results
Fluvoxamine 100mg-300mg/d versus paroxetine 20 mg/d-60 mg/d versus citalopram 20 mg/d-60 mg/d, fixed dosing schedule in obsessive-compulsive disorder[53]	Randomized, single-blind study N=30 10 weeks	NIMH-OC Y-BOCS HAM-D CGI scale	No significant differences between the treatment groups (p=0.000)
Paroxetine 15-60 mg/d versus venlafaxine 75-300 mg/d, fixed dosing schedule in obsessive-compulsive disorder[54]	Randomized, double-blind, controlled parallel-group study N=150 12 weeks	Y-BOCS	Both treatments were significant (p=0.001) No significant effect of drug (p=0.797) No significant effect of drug and time interaction (p= 0.95)
Paroxetine controlled release 12.5 mg/d or 25 mg/d vs. placebo in premenstrual dysphoric disorder[55]	Randomized, double-blind, placebo-controlled trial N=47 3 menstrual cycles	VAS	Paroxetine controlled-release 25 mg was significantly better vs placebo. 25 mg (p<0.001), 12.5mg/d (p=0.013)
Sertraline versus paroxetine versus citalopram in depression, posttraumatic stress disorder or social anxiety disorder[56]	Retrospective cohort study N= 14933 Data gathered from 1/1/99-6/30/02	Persistence Switching Discontinuation	Overall, higher rates of switching and discontinuation and lower rates of persistence for paroxetine vs citalopram and sertraline. Paroxetine (23.79%) vs. sertraline (25.96%); p=0.0093 citalopram (26.56%); p=0.0022 Paroxetine (3.55%) vs sertraline (3.32%); p=0.5076 citalopram (2.78%); p=0.0359 Paroxetine (72.66%) vs sertraline (70.72%) ; p=0.0258 citalopram (70.66%); p= 0.0334
Cochrane Review- including 17 SSRI trials, 3 MAOI (phenelzine) trials, 9 trials with reversible monoamine oxidase inhibitors (moclobemide, brofaromine), 9 trials with "other medications" including benzodiazepines, beta blocker, buspirone, gabapentin, and olanzapine in social anxiety disorder [57]	36 randomized controlled trials N=5264 25 trials were short term (≤14 weeks or less); 7 trials had maintenance component; 8 trials had a relapse component	CGI-I scale	Short term increased effectiveness in treatment response of all medication groups over placebo (p<0.05) SSRIS significantly more effective than moclobemide (p<0.0001) No significant difference between SSRIs and brofaromine (p =0.09)

Study	Methods	Efficacy variables	Results
Nefazodone vs. placebo[58]	Double-blind, placebo-controlled N=120 6 weeks	HAM-D-17, CGI-I	Nefazodone treatment resulted in a significant reduction ($p<.01$) of the 17-item HAM-D-17 total score compared with placebo from the end of the first week of treatment through the end of the study (-12.2 nefazodone vs. -7.7 placebo). At the end of the trial, significantly more nefazodone-treated patients (50%) than placebo treated patients (29%) had responded, as indicated by their CGI-I score ($p=.021$) or by a $\geq$50% reduction in their HAM-D-17 scores ($P=.017$). Patients with dysthymia in addition to major depression also showed significant improvement ($p<.05$) when treated with nefazodone, with significant differences in response rates as early as week 2 and through the end of the trial.
Amitriptyline (AMI) vs. other tricyclics and SSRIs[59]	Review of Cochrane database, Medline, EMBASE, PsycINFO, LILACS, Psyndex, CINAHL, SIGLE from 1966-1998 186 randomized controlled trials, 86 studies comparing AMI with another TCA/heterocyclic	CGI HDRS MADRS	AMI had 2.4% higher responder rate but it was not statistically significant. Tolerability of AMI vs. other TCAs (125 trials) showed that AMI had a 13% higher rate of complaints of side effects (significantly greater OR 0.62, 95% CI 0.53-0.73) but drop outs were 20% and 21.5% for AMI and other TCAs, respectively (Not Statistically Significant - NSS). 17 trials showed that AMI had a 2.8% higher responder rate compared to SSRIs (NSS). 40 trials reviewed showed that AMI had a 29.8% drop out rate compared to a 27.7% rate for SSRIs (OR 0.86, 95% CI 0.75-0.98). The authors concluded that there is a slight numerical advantage in responder rates for AMI vs. TCAs or SSRIs but tolerability is statistically worse.

Study	Methods	Efficacy variables	Results
TCAs vs. SSRIs for depression[60]	MEDLINE search of RCTs of SSRIs vs. TCAs from 1966 to 1997 Meta-analysis of 102 RCTs	HDRS MADRS	Efficacy was based on 102 studies (5533 SSRI pts. and 5173 TCA pts.) Efficacy was determined by comparing the mean reduction in depression scores based upon the HDRS or the MADRS. There was no statistical difference in efficacy between the two groups (effect size -0.03, 95% CI -0.09 to 0.03). TCAs did appear more effective for inpatients (-0.23, 95% CI -0.4 to -0.05). SSRIs were better tolerated with discontinuations due to adverse effects significantly greater in the TCA group (12.4% vs. 17.3%, p<0.0001).
TCAs vs. SSRIs for depression treated in primary care[61]	Search of the Cochrane Collaboration up to April 2002 Meta-analysis of 11 studies	HDRS MADRS	6 studies were used for efficacy. Efficacy was determined by comparing the final mean decrease in continuous depression scale scores such as the HDRS and MADRS. A slight, but non-significant, benefit for TCAs was noted (fixed effects 0.07, 95% CI -0.02 to 0.15). 6 studies were used to assess tolerability. More TCA patients withdrew due to side effects compared to SSRIs (27.9% vs. 20.7%, p=0.0007).
TCAs vs. SSRIs for depression[62]	Medline search of RCT, double-blinded from 1980 to 1996 Meta-analysis of 34 studies	HDRS MADRS	30 studies were used for efficacy. Efficacy was determined by the number of patients considered a responder (50% reduction in HDRS or MADRS). Responder rates for the TCAs were 48.6% and SSRIs 48% (NSS). Drop outs due to adverse effects were 22.4% for TCAs and 15.9% for SSRIs (p<0.01).

Study	Methods	Efficacy variables	Results
Amitriptyline vs. mirtazapine in depressed outpatients[63]	Meta analysis of 4 trials of amitriptyline vs. mirtazapine vs. placebo 4 randomized, DB, placebo controlled 6 week studies	HDRS MADRS	Efficacy was determined by a mean change in HDRS or MADRS from baseline to endpoint. There were 193 placebo patients, 193 AMI patients and 194 mirtazapine patients. Both AMI and mirtazapine showed statistically better improvement in depression compared to placebo ($p<0.05$). There was not a difference in efficacy between AMI and mirtazapine. The number of responders (50% reduction in HDRS or MADRS) was greater in the active treatments compared to placebo ($p<0.05$) as well as the number of remitters (HDRS ≤ 7) ($p<0.05$) but was not different between each other. Drop outs due to adverse effects were greater in the AMI group (17%) compared to the mirtazapine (10%) ($p<0.05$) and placebo (4%) groups ($p<0.05$). Drop outs due to lack of efficacy were greater in the mirtazapine group (15.1%) compared to the AMI group (7.4%) ($p<0.05$). Both active groups were better than placebo (23.7%) ($p<0.05$).
Switch study of imipramine vs sertraline in antidepressant resistant depressed patients[64]	Double-blind N=117 sertraline N=51 imipramine 12 weeks	HDRS	Response was defined as a 50% decrease in the 24 item HDRS. The 2 groups were equal in response rates for completers, 63% and 55% for the sertraline and IMI groups, respectively ($p=0.16$). However, in the ITT analysis there was a statistical better outcome for the sertraline group ($p=0.03$). Those patients going from sertraline to IMI experienced significant increases in 8 adverse events and significant reductions in 3 adverse events while those patients going from IMI to sertraline experienced a significant reduction in 7 adverse events and no increase in any adverse event.

Study	Methods	Efficacy variables	Results
Cochrane analysis of active placebo vs. antidepressants for depression[65]	Medline 1966-2000, Psychlit 1980-2000 and EMBASE 1974-2000 of randomized, controlled trials 9 studies of TCA vs. active placebo (atropine)	Varied among the trials	Efficacy measurements varied among the trials and effect sizes were compared. TCAs were statistically better than active placebo in the pooled analysis (0.39, 95% CI 0.24 to 0.54). The authors concluded that this effect was heterogeneous and that it was smaller than other non-active placebo controlled trials. They suggest that there may be bias in the placebo controlled trials due to unblinding based upon the anticholinergic effects of the TCAs.
Review relapse prevention with anti-depressants[66]	Systematic review and meta-analysis 32 trials of which 15 compared TCAs with placebo for relapse prevention	Proportion of patients relapsing in trials that ranged in length from 6-36 months	In the 15 TCA trials there was a statistically significant reduction in the number of patients that relapsed compared to placebo of 25% vs. 57% ($p<0.00001$). The authors also found that there was no difference in relapse prevention between the different classes of antidepressants.
Clomipramine vs. fluvoxamine for OCD[67]	Randomized, double-blind, 10 week trial N=42 clomipramine, N=37 fluvoxamine	Y-BOCS	Change from baseline in the Y-BOCS was the primary outcome measure. A secondary efficacy measure was percent responders as determined by a 25% reduction on the Y-BOCS. The mean reduction in Y-BOCS for the fluvoxamine group was 30.2% and for the clomipramine group 30.0% (NSS). Responder rates for the fluvoxamine group were 56% and in the clomipramine group were 54% (NSS). 5 and 7 patients dropped out of the study due to adverse events in the fluvoxamine and clomipramine group, respectively.

Study	Methods	Efficacy variables	Results
Bupropion sustained-release vs. sertraline[70]	Randomized, double-blind, parallel-group trial N=248 16 weeks	HAM-D HAM-A CGI-I CGI-S scores	No between-group differences were observed on any of the scales ($p>0.05$). However, side effect profiles differed significantly; Orgasm dysfunction was more common in sertraline-treated patients ($p<0.001$). Nausea, diarrhea, somnolence, and sweating were also experienced more frequently ($p<0.05$) in sertraline-treated patients.
Bupropion sustained-release vs. paroxetine[71]	Randomized, double-blind, multicenter trial N=100 6 weeks	HAM-D HAM-A CGI-I and CGI-S scores	No statistically significant differences between the two groups ($p>0.05$). Somnolence and diarrhea were more common in paroxetine-treated patients ($p<0.05$).
Duloxetine vs. paroxetine vs. placebo[72]	Randomized, double-blind, placebo-controlled, and active comparator-controlled study N=353 8 weeks	HAM-D	Duloxetine 80 mg/d was more effective than placebo($p=0.002$). Duloxetine at 40 mg/d was also significantly more effective than placebo ($p=0.034$). Paroxetine was not more effective than placebo ($p=0.150$). Duloxetine 80 mg/d was more effective than placebo for most other measures, including overall pain severity, and was more effective than paroxetine on HAMD17 ($p=0.037$).
Mirtazapine vs. fluoxetine[73]	Randomized, double-blind trial N=123 6 weeks	HAM-D	The mean HAMD17 scores were no different at week 6 for the two groups; although at week 3 (the estimated treatment difference -3.4 in favor of mirtazapine; 95% CI -6.1,-0.76; $p=0.006$) and week 4 (the estimated treatment difference -3.8 in favor of mirtazapine: 95% CI -6.61,-1.02, $p=0.009$), statistical significance was reported for mirtazapine. No other assessment endpoints were statistically different between the two groups at week 6.
Orally disintegrating mirtazapine vs. sertraline[74]	Randomized, multinational, double-blind trial N=345 8 weeks	HAM-D	Mirtazapine was significantly ($p<0.05$) more effective than sertraline at all assessments during the first 2 weeks of the study. After this time, HAMD total scores were similar in both groups.

Study	Methods	Efficacy variables	Results
Mirtazapine vs. venlafaxine[75]	Randomized, multicenter, double-blind trial N=157 8 weeks	HAM-D MADRS	A statistically significant difference favoring mirtazapine was found on the HAM-D Sleep Disturbance factor at all assessment points ($p \leq 0.03$). A statistically significantly higher percentage of patients treated with venlafaxine (15.3%) than mirtazapine (5.1%) dropped out because of adverse events (p=0.037).
Venlafaxine vs. fluoxetine vs. placebo[76]	Randomized, multicenter, double-blind, placebo-controlled trial N=308 6 weeks	HAM-D	On the HAM-D, overall differences among treatment groups at week 6 did not quite reach statistical significance (p=0.051), though the difference between the venlafaxine and placebo groups was statistically significant (p=0.016). The differences between fluoxetine and placebo (p=0.358) and between venlafaxine and fluoxetine (p=0.130) were not statistically significant. The difference on the HAM-D depressed mood item was statistically significant among treatment groups at week 6 (p<0.001); both active treatments were significantly more effective than placebo (venlafaxine, p<0.001; fluoxetine, p=0.024). The difference between the active treatments was not statistically significant (p=0.117).
Venlafaxine vs. imipramine[77]	Randomized, double-blind, parallel study trial N=167 6 weeks	HAM-D MADRS	No differences in the response rates on the HAM-D or MADRS were observed between treatments. However, among patients who demonstrated a response on the HAM-D, there was a significantly faster onset of response (p=0.036) and sustained response (p=0.018) in the venlafaxine group. The median time to response on the HAM-D among responders was 14 days with venlafaxine and 21 days with imipramine. However, no differences between treatments were observed among responders on the MADRS.

Study	Methods	Efficacy variables	Results
Venlafaxine extended-release vs. fluoxetine vs. placebo[78]	Randomized, multicenter, double-blind, parallel-group, placebo-controlled trial N=301 8 weeks	HAM-D	The percentages of patients who achieved full remission of their depression (HAM D total score ≤7) at the end of treatment were 37%, 22% and 18% for the venlafaxine XR, fluoxetine and placebo groups, respectively. The differences in remission rates between venlafaxine XR and the other groups were statistically significant (p<0.05).
Venlafaxine extended-release 225 mg/day vs. escitalopram 20 mg/day[79]	Randomized, double-blind N=100 venlafaxine extended-release N=98 escitalopram 8 weeks	MADRS	There were no significant differences in efficacy, remission rates or response rates between venlafaxine ER and escitalopram. More patients in venlafaxine ER group had treatment-emergent adverse effects compared to escitalopram (85.0% vs. 68.4%) but this was not statistically significant and may have been due to rapid titration of the venlafaxine dose. Venlafaxine ER had a higher incidence of discontinuation due to adverse events (16% vs. 4.1%; p<.01).

CGI-I=Clinical Global Impressions Improvement scale; CGI-S=Clinical Global Impressions-Severity of Illness scale; HAM-A=Hamilton Rating Scale for Anxiety; HAM-D=Hamilton Rating Scale for Depression; HDRS=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NIMH-OC=National Institute of Mental Health-Obsessive-Compulsive Scale; PAS= Panic and Agoraphobia Scale; VAS=Visual Analog Scale;Y-BOCS=Yale-Brown Obsessive-Compulsive Scale

Additional Evidence

Dose Simplification**:** The dosing schedule of antidepressants varies according to the indication and individual being treated. Many generic antidepressants, including ones from the SSRI and tricyclic antidepressant categories, are available in formulations that can be dosed once a day. A literature search revealed no peer reviewed studies that reported a difference in clinical outcomes based on the antidepressant's dosing schedule or regimen. One randomized, nonblinded trial compared continued compliance rates with fluoxetine 90 mg once-weekly to fluoxetine 20 mg once-daily in patients who had previously received four weeks of fluoxetine 20 mg once-daily.[80] At the end of 12 weeks, compliance rates significantly declined from 87% to 79% with the once-daily fluoxetine; however, the effect on clinical outcomes was not measured. More patients in the once-weekly group discontinued therapy due to lack of efficacy than in the once-daily group but this difference was not statistically significant.

Stable Therapy**:** Although the different SSRIs show similar efficacy, the differences in their adverse event profile may result in patients switching to another agent within the SSRI class, or to another antidepressant class altogether.[68]

In one study which compared fluoxetine, imipramine (IMI) and desipramine (DES) for duration of initial therapy , fluoxetine was taken for a longer period of time than desipramine or imipramine (p<0.001 for either DES or IMI). Statistical comparisons between the two TCAs were not done but they were numerically similar. The difference in duration of therapy was due primarily to less tolerability of desipramine and imipramine. Only 9% of the patients switched from fluoxetine due to adverse events while 27% and 28% assigned to DES and IMI respectively switched due to adverse event (p<0.001 for both

TCAs compared to fluoxetine). The overall length of antidepressant therapy (if the patient switched to another agent) was not different regardless of which agent was initiated initially. In addition, response to medication as measured by the HDRS was equivalent.[81] The authors measured total health care costs and found no difference between the 3 groups.[82]

Impact on Physician Visits: One study comparing health care costs of fluoxetine versus imipramine and fluoxetine versus desipramine compared outpatient costs to primary care and to mental health.[82] The authors found no difference in primary care visit cost in either comparison (fluoxetine versus desipramine p=0.19 and fluoxetine versus imipramine p=0.98). There was also no difference in mental health outpatient visit cost in either comparison group (fluoxetine versus desipramine p=0.33 and fluoxetine versus imipramine p=0.73).[82]

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this AHFS drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current AL Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the AL Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the AL Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0 - $25 per Rx
$$	$26 -$50 per Rx
$$$	$51-$75 per Rx
$$$$	$76-$100 per Rx
$$$$$	$101-$150 per Rx

Rx = prescription

Table 9. Relative Cost Index of Antidepressants

Generic Name	Formulation	Example Brand Name (s)	Brand Cost	Generic Cost
Monoamine Oxidase Inhibitors				
Isocarboxazid	Tablets	Marplan®	$$$	N/A
Phenelzine	Tablets	Nardil®	$$$	N/A
Tranylcypromine	Tablets	Parnate®	$$$	N/A
Selective-serotonin Reuptake Inhibitors				
Citalopram	Solution, tablets	Celexa®*	$$$-$$$$	$
Escitalopram	Solution, tablets	Lexapro®	$$$	N/A
Fluoxetine	Capsules, delayed-release capsules, solution, tablets	Prozac®*, Rapiflux®, Prozac Weekly®, Sarafem®	$$$$-$$$$$	$$

Generic Name	Formulation	Example Brand Name (s)	Brand Cost	Generic Cost
Fluoxetine and olanzapine	Capsules	Symbyax®	$$$$$	N/A
Fluvoxamine	Tablets	Luvox®*^	$$$$	$$$
Paroxetine hydrochloride	Controlled-release tablets, suspension, tablets	Paxil®*, Paxil CR®	$$$-$$$$	$$$
Paroxetine mesylate	Tablets	Pexeva®	$$$	N/A
Sertraline	Solution, tablets	Zoloft®	$$$-$$$$	N/A
Serotonin Modulators				
Nefazodone	Tablets	Serzone®*^	$$$	$$
Trazodone	Tablets	Desyrel®*	$$$$$	$
Tricyclic Antidepressants				
Amitriptyline	Tablets	Elavil®*^, Vanatrip®*	$$$	$
Amitriptyline and chlordiazepoxide	Tablets	Limbitrol®*, Limbitrol DS®*	$$$$	$$
Amitriptyline and perphenazine	Tablets	Etrafon®*, Triavil®*	$$$	$
Amoxapine	Tablets	Asendin®*	$$$$	$
Clomipramine	Capsules	Anafranil®*	$$$$$	$
Desipramine	Tablets	Norpramin®*	$$$$	$$
Doxepin	Capsules, oral concentrate	Adapin®*, Sinequan®*	$$$	$
Imipramine hydrochloride	Tablets	Tofranil®*	$$$$$	$
Imipramine pamoate	Capsules	Tofranil-PM®	$$$$$	N/A
Maprotiline	Tablets	Ludiomil®*	$$$	$
Nortriptyline	Capsule, solution	Aventyl®*, Pamelor®*	$$$$$	$
Protriptyline	Tablets	Vivactil®	$$$$	N/A
Trimipramine	Capsules	Surmontil®	$$$	N/A
Miscellaneous Antidepressants				
Bupropion	Extended-release tablets, sustained-release tablets, tablets	Wellbutrin®*, Wellbutrin SR®*, Wellbutrin XL®	$$$$	$$$
Duloxetine	Capsules	Cymbalta®	$$$$	N/A
Mirtazapine	Orally disintegrating tablets, tablets	Remeron®*, Remeron SolTab®*	$$$	$$
Venlafaxine	Sustained-release capsules, tablets	Effexor®, Effexor XR®	$$$-$$$$	NA

*Generic is available.
^Brand is no longer available.

X. Conclusions

Clinical studies support that antidepressants are of equivalent efficacy when administered in comparable doses. The choice of an antidepressant is influenced by the patient's diagnosis, current medical history, past history of response, the potential for drug-drug interactions, and the adverse events profile.[43] Treatment failure to one antidepressant class or specific antidepressant within a class does not predict treatment failure to another drug class or antidepressant. [43]

The SSRIs appear to be better tolerated than the tricyclic and other norepinephrine-reuptake inhibitors but the long term risk of relapse is comparable. Both are statistically better than placebo.[65] The MAOIs are effective treatments for patients with major depressive disorder; however, drug-interactions, dietary restrictions, and side-effects greatly limit their use. Although the MAOIs have been used in clinical practice for many years, there are limited head-to-head trials comparing these agents with each other and with the newer antidepressant classes. Firm conclusions about the relative efficacy of the approved MAOIs could not be made.

All brand products within the antidepressant class, with the exception of the monoamine oxidase inhibitors, are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand monoamine oxidase inhibitor is recommended for preferred status, regardless of cost.

No brand antidepressant is recommended for preferred status. Alabama Medicaid should accept cost proposals (except as noted for the monoamine oxidase inhibitors) from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics
Barbiturates AHFS Class 282404
December 14, 2005

I. Overview

Developed in the early 1900's, barbiturates were some of the earliest sedative-hypnotics and were widely used throughout the first half of the 20th century. Though their exact mechanism of action is not fully understood, the pharmacologic properties of barbiturates appear to be related to the activation of γ-aminobutyric acid (GABA) and inhibition of excitory glutamate receptors.[1]

The barbiturates have been employed primarily as sedative-hypnotics for short-term treatment of insomnia and induction of daytime sedation. They have also served as adjuncts to anesthesia and as agents for the treatment of seizure disorders. Despite this extensive usage in the past, the barbiturates have the disadvantage of abuse and addiction potential. In addition, they have many unfavorable side effects and have a narrow therapeutic range with a low therapeutic index. Due to these safety issues, at present barbiturates have been largely replaced by newer and safer agents, most notably the benzodiazepines. Today, barbiturates are used occasionally, mostly for anesthesia, the treatment of seizure disorder, and alcohol detoxification.[1-4]

This review encompasses all dosage forms and strengths. (See Table 1.)

Table 1. Barbiturates Included in this Review

Generic Name	Formulation	Example Brand Name(s)
Amobarbital	Injection	Amytal®
Amobarbital/Secobarbital	Capsules†	Tuinal®
Butabarbital	Elixir, tablet	Butisol®*
Mephobarbital	Tablets	Mebaral®
Methohexital	Injection	Brevital®
Pentobarbital	Injection, capsules†, elixir†, and suppositories†	Nembutal®*
Phenobarbital	Elixir, injection, tablet	Luminal®*
Secobarbital	Capsule, injection†	Seconal®

*Generic is available in at least one dosage form or strength.
† Product is no longer available in this dosage form.

II. Evidence Based Medicine and Current Treatment Guidelines

Table 2 provides a brief overview of the treatment guidelines for those conditions for which barbiturates may be indicated.

Table 2. Treatment Guidelines for the Barbiturates[5-7]

Clinical Guideline	Recommendation
Standards of Practice Committee of the America Academy of Sleep Medicine: **Nonpharmacologic Treatment of Chronic Insomnia**[5]	**Standard:** generally accepted patient-care strategy which reflects a high degree of clinical certainty Stimulus control Training that re-associates the bed and bedroom with rapid sleep onset

Clinical Guideline	Recommendation
	Guideline: patient-care strategy which reflects a moderate degree of clinical certainty Progressive muscle relaxation Method of tensing and relaxing muscles Paradoxical intention Patients attempt to stay awake Biofeedback Visual or auditory feedback to reduce somatic arousal **Option:** patient-care strategy which reflects uncertain clinical use Sleep restriction Limit amount time spent in bed to actual time spent asleep Multi-component cognitive behavioral therapy Combined therapies which may include stimulus control, progressive muscle relaxation or sleep restriction as a single therapy
American Society of Addiction Medicine Committee on Practice Guidelines: **Pharmacological Management of Alcohol Withdrawal**[6]	**Mild symptoms** (Clinical Institute Withdrawal Assessment-Alcohol, revised score [CIWA-Ar] <8-10) Supportive nonpharmacological therapy and continued monitoring **Moderate symptoms (CIWA-Ar=8-15)** Supportive nonpharmacological therapy and continued monitoring Addition of medications to control symptoms Benzodiazepines* (first-line option) Phenobarbital (second-line option) **Severe symptoms (CIWA-Ar >15)** Supportive nonpharmacological therapy and continued monitoring Addition of medications to control symptoms Benzodiazepines* (first-line option) Phenobarbital (second-line option) **History of withdrawal seizures or notable comorbid medical illness** Initiate a recommended medication regardless of symptom severity Benzodiazepines* (first-line option) Phenobarbital (second-line option) *Trials reviewed by the committee indicate that the benzodiazepines studied are equally effective in reducing signs and symptoms of withdrawal.
The Status Epilepticus Working Party: **Convulsive Status Epilepticus**[7]	**Intravenous (IV) Access** Lorazepam 0.1 mg/kg IV, repeat once if seizing at 10 minutes. If still seizing at 10 minutes then, Phenytoin 18 mg/kg or phenobarbitone 20 mg/kg AND paraldehyde 0.4 mL/kg rectally (PR). If still seizing at 10 minutes Rapid sequence induction of anesthesia using thiopentone 4 mg/kg IV **No IV Access** Diazepam 0.5 mg/kg PR, if still seizing at 10 minutes and still no IV access then, Paraldehyde 0.4 mL/kg PR if still seizing at 10 minutes and IV access, Phenytoin 18 mg/kg or phenobarbitone 20 mg/kg AND paraldehyde 0.4 mL/kg rectally (PR). If still seizing at 10 minutes, Rapid sequence induction of anesthesia using thiopentone 4 mg/kg IV

III. Indications

Table 3. Comparison of FDA-Approved Indications for the Barbiturates[2-4]

Drug	FDA-approved indications
Amobarbital	Premedication for anesthetic procedure Short-term treatment of insomnia
Butabarbital	Preoperative sedation Short-term treatment of insomnia
Mephobarbital	Generalized tonic-clonic seizures and absence seizures Sedative for relief of anxiety, tension and apprehension
Methohexital	Adjunct to general anesthesia Induction of general anesthesia
Pentobarbital	Short-term treatment of insomnia Preoperative sedation Emergency control of acute convulsive episodes
Phenobarbital	Short-term treatment of insomnia Preoperative sedation Partial and generalized seizure disorders
Secobarbital	Short-term treatment of insomnia Preoperative sedation

IV. Pharmacokinetics

Table 4. Pharmacokinetics of the Barbiturates[2-4]

Drug	Amobarbital	Butabarbital	Mephobarbital	Methohexital
Duration of action	Intermediate	Intermediate	Long	Short
Bioavailability	N/A	N/A	50%	N/A
Protein binding	N/A	N/A	N/A	N/A
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic
Active Metabolites	Yes; 3-hydroxy-amobarbital and N-hydroxyamobarbital	nd	Yes; phenobarbital	nd
Elimination	Fecal (4-5%)/ Renal (79-92%)	Renal (nd)	Renal (nd)	Renal (nd)
Half-Life (h=hours)	8-42 h	34-100 h	11-67 h	3.9 h

N/A-not available; nd=no data

Table 4. (continued)

Drug	Pentobarbital	Phenobarbital	Secobarbital
Duration of action	Short	Long	Short
Bioavailability	95%	80-100%	90%
Protein binding	5%	20-60%	52-57%
Metabolism	Hepatic	Hepatic	Hepatic
Active Metabolites	nd	None	Yes
Elimination	Renal (nd)	Renal (21%)	Renal (nd)
Half-Life (h=hours)	15-48 h	1.5-4.9 days	19-34 h

N/A-not available; nd=no data

V. Drug Interactions

Table 5. Significant Drug-Drug Interactions with the Barbiturates[2]

Precipitant Drug	Object Drug	Direction*	Significance Level	Description
Alcohol	Barbiturates	↑	1	Concomitant use may produce additive CNS effects and death.
Charcoal	Barbiturates	↓	2	Charcoal can reduce the absorption of barbiturates. Depending on the clinical situation, this will reduce their efficacy or toxicity.
Valproic acid	Barbiturates	↑	2	Valproic acid appears to decrease barbiturate metabolism, resulting in an increased effect.
Barbiturates	Anticoagulants	↓	1	Barbiturates can increase metabolism of anticoagulants resulting in a decreased response. Patients stabilized on anticoagulants may require dosage adjustments if barbiturates are added to or withdrawn from their regimen.
Barbiturates	Beta blockers	↓	2	Pharmacokinetic parameters of certain β-blockers (metoprolol and propranolol) may be altered by barbiturates. Timolol does not appear to be affected.
Barbiturates	Contraceptives, oral	↓	1	Decreased contraceptive effect may occur due to induction of microsomal enzymes. Menstrual irregularities (spotting, breakthrough bleeding) or pregnancy may occur. An alternate form of birth control is suggested.
Barbiturates	Corticosteroids	↓	2	Barbiturates may enhance corticosteroid metabolism through the induction of hepatic microsomal enzymes
Barbiturates	Doxycycline	↓	2	Phenobarbital decreases doxycycline's half-life and serum levels, which may persist for 2 weeks after barbiturate therapy is discontinued.
Barbiturates	Felodipine	↓	2	Felodipine plasma levels and bioavailability may be reduced.
Barbiturates	Griseofulvin	↓	2	Phenobarbital appears to interfere with the absorption of oral griseofulvin, thus decreasing its blood level; however, the effect on therapeutic response has not been established.
Barbiturates	Methoxyflurane	↑	2	Enhanced renal toxicity may occur.
Barbiturates	Metronidazole	↓	2	Barbiturates may decrease the antimicrobial effectiveness of metronidazole.
Barbiturates	Narcotics	↔	2	Methadone actions may be reduced. CNS depressant effects of meperidine may be prolonged.

Precipitant Drug	Object Drug	Direction*	Significance Level	Description
Barbiturates	Quinidine	↓		Phenobarbital may significantly reduce the serum levels and half-life of quinidine.
Barbiturates	Theophylline	↓	2	Barbiturates decrease theophylline levels, possibly resulting in decreased effects.

*↓=Object drug decreased. ↑=Object drug increased. ↔=Undetermined clinical effect
Significance Level 1: Major severity
Significance Level 2: Moderate severity

VI. Adverse Drug Events

Table 6. Adverse Drug Events Associated with Barbiturates[2-4]

Body System	Adverse Event
Central nervous system	Agitation Anxiety CNS depression Confusion Drowsiness Fever (more prevalent with phenobarbital use) Insomnia Somnolence Vertigo
Gastrointestinal system	Constipation Diarrhea Nausea/vomiting
Cardiovascular system	Bradycardia Hypotension Syncope
Miscellaneous	Hypersensitivity reactions Hypoventilation Respiratory depression

Dependence[1-4]
Barbiturates may be habit-forming; dependence is most commonly seen with short acting agents after prolonged use (> 90 days). Barbiturates should be avoided in patients with a history of substance abuse, especially alcohol abuse, due to synergistic effects and the increased potential of overdose.

Discontinuation[1-4]
Patients who abruptly discontinue barbiturates after prolonged use may experience withdrawal symptoms. Common withdrawal symptoms include:

Minor withdrawal:	
Anxiety Muscle twitches Weakness Tremors	Dizziness Nausea/vomiting Insomnia Orthostatic hypotension
Major withdrawal:	
Seizure Coma	

Major withdrawal symptoms may occur within 16 hours of discontinuation and may last up to 5 days. Avoidance of withdrawal symptoms is best achieved by slow and gradual taper which should be

individualized to the patient and take into consideration the duration of therapy, concomitant illness, and daily dose.

Overdose[1-4]

As noted earlier, barbiturates have a narrow therapeutic index and the risk of overdosage is much greater than with newer sedative-hypnotics. Overdosage risk is also substantially increased in the presence of any other CNS depressant, especially alcohol. The lethal dose of barbiturates can vary; however, single doses of 2-10 g are often fatal. Common overdose symptoms include:

CNS depression Hypotension Lower body temperature	Oliguria Respiratory depression Tachycardia

Treatment of an overdose is primarily supportive, with hemodialysis for severely intoxicated patients. Emesis may be induced in conscious patients, or administration of activated charcoal may accelerate the elimination of barbiturates.

VII. Dosing and Administration

Table 7. Usual Dosing for the Barbiturates[2-4]

	Usual Adult Dose	Usual Pediatric Dose	Availability
Amobarbital	• Insomnia, short term therapy: 65-200 mg IM/IV at bedtime • Premedication for anesthetic procedure: 65-500 mg IM/IV • Seizure: 65-500 mg IV	• Insomnia, short term therapy: (up to 6 yr of age) 2-3 mg/kg/dose IM • Insomnia, short term therapy: (age 6 yr and older) 2-3 mg/kg IM OR 65-500 mg/dose IV • Premedication for anesthetic procedure: 3-5 mg/kg IV OR 65-500 mg IV • Seizure: (under 6 yr of age) 3-5 mg/kg/dose IV/IM • Seizure: (age 6 yr and older) 65-500 mg/dose IV	Vial: 500 mg
Butabarbital	• Insomnia, short term treatment: 50-100 mg orally at bedtime • Preoperative sedation: 50-100 mg orally 60-90 min before surgery • Sedation: daytime, 15-30 mg orally 3 or 4 times daily	• Preoperative sedation: 2-6 mg/kg orally 60-90 min before surgery; MAX 100 mg • Sedation: daytime, 2 mg/kg orally 3 times daily	Elixir: 30 mg/5 mL Tablet: 30 mg, 50 mg
Mephobarbital	• Sedation: daytime, 32-100 mg orally 3 or 4 times daily • Seizure: 400-600 mg in divided doses	• Sedation: daytime, 16-32 mg orally 3-4 times daily • Seizure: (under 5 years of age) 16-32 mg orally 3 to 4 times daily • Seizure: (age 5 years and older) 32-64 mg orally 3 to 4 times daily	Tablet: 32 mg, 50 mg, 100 mg
Methohexital	• General anesthesia; Adjunct: intermittent IV injections of 20-40 mg (2-4 mL of a 1% solution) every 4-7 minutes as needed OR by continuous IV drip of 3 mL/min (0.2% solution) • Induction of general anesthesia: 1-1.5 mg/kg (50-120 mg, mean 70 mg) IV administered at a rate of 1 mL every 5 seconds (1% solution) which usually provides anesthesia for 5-7 minutes	• Induction of general anesthesia: 6.6-10 mg/kg IM (5% concentration) OR 25 mg/kg rectally (1% solution)	Vial: 500 mg, 2.5 g

	Usual Adult Dose	Usual Pediatric Dose	Availability
Pentobarbital	• Insomnia: short-term treatment, 100 mg orally at bedtime • Insomnia: short-term treatment, 120-200 mg rectally at bedtime • Insomnia: short-term treatment, 100 mg IV initially; after 1 min, may give additional small doses at 1 min intervals, if necessary, up to total of 500 mg • Insomnia: short-term treatment, 150-200 mg IM • Preoperative sedation: 100 mg orally • Preoperative sedation: 150-200 mg IM • Sedation: daytime, 20 mg orally, 3-4 times daily • Sedation: daytime, 30 mg rectally, 2-4 times daily • Seizure: 100 mg IV initially; after 1min, may give additional small doses at 1 min intervals, if necessary, up to total of 500 mg	• Insomnia: short-term treatment, ORAL dosage must be individualized by physician • Insomnia: short-term treatment (age 2 months to 1 yr; weight 4.5-9 kg) 30 mg rectally • Insomnia: short-term treatment, (age 1-4 yr; weight 9-18 kg) 30 or 60 mg rectally • Insomnia: short-term treatment, (age 5-12 yr; weight 18-36 kg) 60 mg rectally • Insomnia: short-term treatment, (age 12-14 yr; weight 36-50 kg) 60 or 120 mg rectally • Insomnia: short-term treatment, 2-6 mg/kg IM; MAX 100 mg/dose • Insomnia: short-term treatment, 50 mg IV initially; after 1 min, may give additional small doses at 1 min intervals, if necessary, until desired effect • Preoperative sedation: 2-6 mg/kg IM/ORAL; MAX 100 mg/dose • Preoperative sedation: (age 2 months to 1 yr) 30 mg rectally • Preoperative sedation: (age 1-4 yr) 30 or 60 mg rectally • Preoperative sedation: (age 5-12 yr) 60 mg rectally • Preoperative sedation: (age 12-14 yr) 60 or 120 mg rectally • Sedation: daytime, 2-6 mg/kg/day orally • Sedation: daytime, 2 mg/kg OR 60 mg/m(2) rectally 3 times daily • Seizure: 50 mg IM/IV initially; after 1 min, additional small doses may be administered at 1 min intervals, if necessary, until desired effect	Vial: 50 mg/mL

	Usual Adult Dose	Usual Pediatric Dose	Availability
Phenobarbital	• Alcohol withdrawal-induced convulsion: 260 mg IV, followed by 130 mg IV every 30 minutes as needed to achieve light sedation; MAX 24 hour dosage is 600 mg • Generalized seizure: 60-250 mg/day orally (single or divided doses) OR 100-320 mg IV repeated if necessary up to a MAX total dose of 600 mg/day • Hyperbilirubinemia: 30-60 mg orally 3 times a day • Insomnia: 100-320 mg orally, IM, OR IV at bedtime • Partial seizure: 60-250 mg/day orally (single or divided doses) OR 100-320 mg IV repeated if necessary up to a MAX total dose of 600 mg/day • Preoperative sedation: 130-200 mg IM 60-90 minutes before surgery • Sedated, daytime: 30-120 mg/day orally, IM, OR IV in 2-3 divided doses • Status epilepticus: 10-20 mg/kg by slow IV, repeated if necessary	• Drug withdrawal syndrome in newborn–Opioid withdrawal: 8-10 mg/kg/day orally OR IM for 2 days, then 5-6 mg/kg/day orally OR IM, then taper the dose over 7-10 days OR 3-10 mg/kg/day orally until withdrawal symptoms are relieved, then gradually decrease the dosage and completely withdraw the drug over a 2-week period • Febrile seizure; Prophylaxis: infants and children, 15-20 mg/kg orally followed by 3-6 mg/kg/day (single or divided dose) • Generalized seizure: less than 1 month old, 2.9-4.9 mg/kg/day IV (single or divided dose); monitor phenobarbital levels carefully and adjust the dose accordingly • Generalized seizure: more than 1 month old, 6 mg/kg/day IV (single or divided dose); monitor phenobarbital levels carefully and adjust the dose accordingly • Hyperbilirubinemia: neonates, 5-10 mg/kg/day orally or IM for the first few days after birth • Hyperbilirubinemia: 1-4 mg/kg 3 times a day • Partial seizure: less than 1 month old, 2.9-4.9 mg/kg/day IV (single or divided dose); monitor phenobarbital levels carefully and adjust the dose accordingly • Partial seizure: more than 1 month old, 6 mg/kg/day IV (single or divided dose); monitor phenobarbital levels carefully and adjust the dose accordingly • Preoperative sedation: 1-3 mg/kg orally, IM, OR IV 60-90 min before surgery • Sedated, Daytime: 2 mg/kg OR 60mg/m(2) of body surface area orally 3 times a day • Status epilepticus: 15-20 mg/kg IV over a period of 10-15 minutes	Elixir: 20 mg/5 mL Disposable syringe/vial: 65 mg/mL, 130 mg/mL Tablet: 15 mg, 16.2 mg, 30 mg, 32.4 mg, 60 mg, 64.8 mg, 97.2 mg, 100 mg

	Usual Adult Dose	Usual Pediatric Dose	Availability
Secobarbital	• Insomnia, short-term treatment: 100 mg orally at bedtime • Insomnia, short-term treatment: 100-200 mg IM • Insomnia, short-term treatment: 50-250 mg IV • Premedication for anesthetic procedure: 200-300 mg orally 1-2 hr before surgery • Sedation: daytime, 30-50 mg orally 3-4 times daily • Sedation: dentistry, 1.1-2.2 mg/kg IM 10-15 min before procedure • Sedation: nerve block, 100-150 mg IV • Seizure: 5.5 mg/kg IM/IV, repeat every 3-4 hr as needed	• Insomnia, short-term treatment: 3-5 mg/kg OR 125 mg/m(2) IM, MAX 100 mg/dose • Insomnia, short-term treatment: (weight up to 40 kg) 5 mg/kg rectally as 1-1.5% solution • Insomnia, short-term treatment: (weight 40 kg and over) 4 mg/kg rectally as 1-1.5% solution • Premedication for anesthetic procedure: 2-6 mg/kg orally 1-2 hr before surgery; MAX dose 100 mg • Premedication for anesthetic procedure: 4-5 mg/kg IM • Sedation: daytime, 2 mg/kg OR 60 mg/m(2) orally 3 times daily • Seizure3-5 mg/kg/dose OR 125 mg/m(2)/dose IM/IV	Capsule: 100 mg

VIII. Effectiveness

Though the barbiturates as a class have been used for over a century, limited direct comparison trials are available for the treatment of FDA-approved indications. Table 8 below summarizes studies conducted with barbiturates.

Table 8. Outcomes Evidence for the Barbiturates

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Mello de Paula et al.[8]	Double-blind, randomized trial	Adult patients with insomnia	60	Zopiclone* 7.5 mg Pentobarbital 100 mg Placebo	16 nights	• Both zopiclone and pentobarbital had significant improvement compared to placebo in improved sleep onset, duration of sleep, quality of sleep and number of awakenings ($p<0.001$) • Zopiclone had significant improvement compared to pentobarbital in sleep quality and condition in morning ($p< 0.05$) • Fewer side effects experienced in zopiclone group ($p<0.05$)
Okawa et al.[9]	3 randomized, crossover trials	Adult patients with insomnia	75	Triazolam 0.5 mg Secobarbital 100 mg Placebo	2 nights	• Significant improvement in triazolam group compared to secobarbital ($p<0.001$) and placebo ($p\leq 0.002$) in sleep onset, duration of sleep and number of awakenings • Triazolam preferred agent of study subjects ($p< 0.001$)
Painter et al.[10]	Single-blind, randomized trial	Neonates admitted into ICU with seizures	59	Phenytoin Phenobarbital Phenobarbital/phenytoin	Not specified	• Phenobarbital controlled seizures in 43% of patients • Phenytoin controlled seizures in 45% of patient • Difference between phenytoin and phenobarbital not significant ($p=1.0$)

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Treiman et al.[11]	Double-blind, randomized trial	Patients with overt or subtle status epilepticus	384	Lorazepam Diazepam/phenytoin Phenobarbital Phenytoin	5 years	• Treatment success (%) in overt status epilepticus - Lorazepam (64.9%), phenobarbital (58.2%), diazepam/phenytoin (55.8%) and phenytoin (43.6%) • Lorazepam had significantly higher treatment success compared to phenytoin ($p<0.02$) • No significant differences between other groups • Treatment success (%) subtle status epilepticus - Lorazepam (17.9%), phenobarbital (24.2%), diazepam/phenytoin (8.3%) and phenytoin (7.7%) • No significant differences between treatment groups

***** Not available in US

Additional Evidence

Dose Simplification: Since the barbiturates are used to treat several disorders, dosages must be individualized per condition. A literature search of Medline and Ovid did not reveal clinical studies on dose simplification in relation to the barbiturates.

Stable Therapy: A literature search of Medline and Ovid did not reveal clinical studies that have investigated the effect of changing from one barbiturate to another.

Impact on Physician Visits: A literature search of Medline and Ovid did not reveal clinical studies that have evaluated the impact of use of these drugs on physician visits.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this AHFS drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current AL Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the AL Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the AL Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0 - $25 per Rx
$$	$26 -$50 per Rx
$$$	$51-$75 per Rx
$$$$	$76-$100 per Rx
$$$$$	$101-$150 per Rx

Rx = prescription

Table 9. Relative Cost of Anxiolytics, Sedatives, and Hypnotics: Barbiturates

Generic Name	Form	Example Brand Name(s)	Brand Cost	Generic Cost
Amobarbital	Injection	Amytal®	$$$	N/A
Butabarbital	Elixir, tablet	Butisol®*	$$$$	N/A
Mephobarbital	Tablet	Mebaral®	$$$	N/A
Methohexital	Injection	Brevital®	$$	N/A
Pentobarbital	Injection	Nembutal®*	$$	N/A
Phenobarbital	Elixir, tablet, injection	Luminal®*^	$$$	$
Secobarbital	Capsule	Seconal®	$	N/A

*Generic is available in at least one dosage form or strength.
^ Brand name is only available as injection.
N/A = not available

X. Conclusions

Though barbiturates, among the earliest sedative-hypnotics, were widely used during the early 20th century, safety and abuse issues coupled with the availability of newer and safer agents have limited their use in the outpatient setting in recent years. Currently, no clinical guideline recommends a barbiturate as a first-line therapy option for any condition in an outpatient setting. Barbiturate use in insomnia is limited to short-term use only and the limited trials available suggest that they are not as effective as other sedative-hypnotics. All of the barbiturates are primarily metabolized via hepatic enzymes and elderly patients and patients with hepatic insufficiency are more susceptible to class related adverse effects.

Within the limited range of published, peer-reviewed, clinical trials for this class, there is insufficient evidence that demonstrates that one agent is more efficacious or safer than another. In general, the barbiturates should not be considered as a first-line therapy choice for any indication.

Therefore all brand products are comparable to each other and the generic products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand barbiturate is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics
Benzodiazepines AHFS Class 282408
December 14, 2005

I. Overview

Benzodiazepines have been a mainstay of pharmacological treatment for anxiety disorders and insomnia since first introduced in the 1960's. These agents have largely replaced the barbiturates for the management of anxiety and insomnia since they have a better safety and tolerability profile compared to the barbiturates.[1] In addition to the short-term treatment of insomnia and anxiety disorders, benzodiazepines have been used as adjunctive therapy in seizure disorders, management of acute alcohol withdrawal, preoperative sedation and emergency intervention of convulsive status epilepticus.[2-6]

Primary insomnia, as defined by *The Diagnostic and Statistical Manual of Mental Disorders,* is difficulty in initiating or maintaining sleep for at least one month, causing marked distress or impairment in social, occupational, or other important areas of functioning. The disturbance of sleep (or associated daytime fatigue) is not due to another sleep disorder such as narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder and parasomnia. A sleep disturbance that occurs exclusively during the course of a mental disorder (e.g. major depressive disorder, generalized anxiety disorder or delirium) or one that is due to a medication, drug of abuse, or general medical condition, is also not considered a diagnosis of primary insomnia.[1] Essentially, a diagnosis of primary insomnia is made after other possible mental and medical disorders have been excluded.

Management of insomnia is most effective when the choice of treatment is patient-specific taking into consideration age, duration of symptoms, severity and etiologies. For many patients, treatment of insomnia with non-pharmacological behavioral changes may be as effective as drug therapy.

Anxiety states are a collection of conditions in which a generalized pervasive fear dominates a patient's life. Anxiety disorders include the following: generalized anxiety disorder, obsessive compulsive disorder, panic disorder, post-traumatic stress, and social phobias.[7]

Benzodiazepines are non-selective full agonists of the benzodiazepine receptors. Within the body, there are 3 major benzodiazepine receptor subtypes. Benzodiazepine receptor subtype-1 is located throughout the central nervous system (CNS) and is thought to mediate anxiolytic, sedative and anticonvulsant properties of the benzodiazepines. Benzodiazepine receptor subtype-2 is located in the cortex, hippocampus, striatum, and spinal cord and is believed to mediate muscle relaxation, CNS depression, and psychomotor impairment. Benzodiazepine receptor subtype-3 is located throughout the body as well as the glial cells and is believed to contribute to tolerance and withdrawal when activated. When bound to benzodiazepine receptors, the effects of γ-aminobutyric acid (GABA) and other inhibitory neurotransmitters are potentiated.[2-6]

This review encompasses all dosage forms and strengths. (See Table 1.) Currently, Alabama Medicaid does not cover alprazolam, estazolam, halazepam, and quazepam formulations as benzodiazepines are an excludable drug class in accordance with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90).

Table 1. Benzodiazepines Included in this Review[2-6]

Generic Name	Formulation	Example Brand Name(s)
Alprazolam^	Oral concentrate, orally disintegrating tablet, tablet, extended-release tablet	Xanax®*, Niravam®, Xanax XR®
Chlordiazepoxide	Capsule, injection	Librium®*
Chlordiazepoxide/clidinium	Capsule	Librax®*
Clonazepam	Tablet, orally disintegrating tablet	Klonopin®*, Klonopin Wafers®
Clorazepate	Tablet	Tranxene T-Tab®*
Clorazepate	Tablet, extended-release	Tranxene SD®
Diazepam	Injection, solution, tablet	Valium®*^
Diazepam	Rectal gel	Diastat®
Estazolam^	Tablet	Prosom®*
Flurazepam	Capsule	Dalmane®*
Halazepam‡^	Tablet	Paxipam®
Lorazepam	Injection, oral concentrate, tablet	Ativan®*
Midazolam	Injection, syrup	Versed®
Oxazepam	Capsule	Serax®*
Quazepam^	Tablet	Doral®
Temazepam†	Capsule	Restoril®*
Triazolam	Tablet	Halcion®*

*Generic is available in at least one dosage form or strength.
† Generic is not available for 7.5 and 22.5 mg strengths.
‡ Product was discontinued by manufacturer.
^Product is currently not covered by Alabama Medicaid.

II. Evidence Based Medicine and Current Treatment Guidelines

Table 2 is a brief representation of treatment guidelines concerning benzodiazepines.

Table 2. Treatment Guidelines Using the Benzodiazepines

Clinical Guideline	Recommendation
Standards of Practice Committee of the America Academy of Sleep Medicine: **Nonpharmacologic Treatment of Chronic Insomnia[8]**	**Standard:** generally accepted patient-care strategy which reflects a high degree of clinical certainty Stimulus control Training that re-associates the bed and bedroom with rapid sleep onset **Guideline:** patient-care strategy which reflects a moderate degree of clinical certainty Progressive muscle relaxation Method of tensing and relaxing muscles Paradoxical intention Patients attempt to stay awake Biofeedback Visual or auditory feedback to reduce somatic arousal **Option:** patient-care strategy which reflects uncertain clinical use Sleep restriction Limit amount time spent in bed to actual time spent asleep Multi-component cognitive behavioral therapy Combined therapies which may include stimulus control, progressive muscle relaxation or sleep restriction as a single therapy

Clinical Guideline	Recommendation
National Institutes of Health (NIH) State-of-the-Science Conference Statement: **Chronic Insomnia in Adults**[9]	**Conference statement:** "Evidence supports the efficacy of cognitive-behavioral therapy and benzodiazepine receptor agonists in the treatment of this disorder (chronic insomnia), at least in the short term. Very little evidence supports the efficacy of other treatments, despite their widespread use."
Consensus Statement from the International Consensus Group on Depression and Anxiety: **Panic Disorder**[10]	**Acute** **First line:** SSRIs, initiated at low dose. **Second line:** Concomitant use of a benzodiazepine for a limited period (< 8 weeks) may be considered to help initiate treatment with a SSRI. **Maintenance** Limited evidence suggests that once patient is in full remission, the therapeutic dose may be reduced slowly. **Second line (non-responders):** If patient fails to respond at the maximum tolerated dose of a SSRI, or if partial response was observed and the SSRI well tolerated, switch to another SSRI. If SSRI not tolerated, initiate trial with a benzodiazepine or tricyclic antidepressant (TCA). **Third line:** Monoamine oxidase inhibitor (MAOI) or valproate. **Duration of treatment:** 8 to 12 weeks of treatment is considered an adequate trial. If remission is maintained, consider stopping treatment after 12-24 months.
Consensus Statement from the International Consensus Group on Depression and Anxiety: **Generalized Anxiety Disorder (GAD)**[11]	**First line:** Antidepressants–SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs) or least-sedating TCAs. **Second line:** Buspirone **Adjunct therapies:** • Benzodiazepines: consider as first-line therapy agent in an acute anxiety reaction. Use as adjunct agent in acute exacerbations of GAD or sleep disturbances during the initiation of antidepressant therapy. Patient should be stabilized on antidepressant therapy for > 4 weeks before benzodiazepines are slowly tapered (over 4-8 weeks). • Hydroxyzine: consider use in acute anxiety states.
Consensus Statement from the International Consensus Group on Depression and Anxiety: **Social Anxiety Disorder (SAD)**[12]	**Pharmacological treatment recommendation**: SSRI. Most studies conducted with paroxetine. Dose should be initiated at 20 mg/day for 2-4 weeks and then titrated to obtain a response. **Duration of treatment:** Adequate trial of therapy requires 6 to 8 weeks of treatment. If treatment is effective and remission maintained, minimum duration of therapy is 12 months. Note: there is no clinical evidence that benzodiazepines, TCA, or β-blockers as a class are effective for treatment of social anxiety disorder.

Clinical Guideline	Recommendation
American Society of Addiction Medicine Committee on Practice Guidelines: **Pharmacological Management of Alcohol Withdrawal**[13]	**Mild symptoms** (Clinical Institute Withdrawal Assessment-Alcohol, revised score [CIWA-Ar] <8-10) Supportive nonpharmacological therapy and continued monitoring **Moderate symptoms (CIWA-Ar=8-15)** Supportive nonpharmacological therapy and continued monitoring Addition of medications to control symptoms Benzodiazepines* (first-line option) Phenobarbital (second-line option) **Severe symptoms (CIWA-Ar >15)** Supportive nonpharmacological therapy and continued monitoring Addition of medications to control symptoms Benzodiazepines* (first-line option) Phenobarbital (second-line option) **History of withdrawal seizures or notable comorbid medical illness** Initiate a recommended medication regardless of symptom severity Benzodiazepines* (first-line option) Phenobarbital (second-line option) *Trials reviewed by the committee indicate that the benzodiazepines studied are equally effective in reducing signs and symptoms of withdrawal.
The Status Epilepticus Working Party: **Convulsive Status Epilepticus**[14]	**Intravenous (IV) Access** Lorazepam 0.1 mg/kg IV, repeat once if seizing at 10 minutes. If still seizing at 10 minutes then: Phenytoin 18 mg/kg or phenobarbitone 20 mg/kg AND paraldehyde 0.4 mL/kg rectally (PR). If still seizing at 10 minutes: Rapid sequence induction of anesthesia using thiopentone 4 mg/kg IV **No IV Access** Diazepam 0.5 mg/kg PR, if still seizing at 10 minutes and still no IV access then: Paraldehyde 0.4 mL/kg PR if still seizing at 10 minutes and IV access Phenytoin 18 mg/kg or phenobarbitone 20 mg/kg AND paraldehyde 0.4 mL/kg rectally (PR). If still seizing at 10 minutes: Rapid sequence induction of anesthesia using thiopentone 4 mg/kg IV

III. Indications

Table 3. FDA-Approved Indications for the Benzodiazepines[1-6]

Drug	FDA-Approved Indications
Alprazolam^	Panic disorder with or without agoraphobia Management of anxiety disorders
Chlordiazepoxide	Management of anxiety disorders Acute alcohol withdrawal Preoperative apprehension and anxiety
Clorazepate	Management of anxiety disorders Acute alcohol withdrawal Adjunct therapy for partial seizures
Chlordiazepoxide/ clidinium	Adjunct therapy in the treatment of peptic ulcer Adjunct treatment of the irritable bowel syndrome Adjunct treatment of acute enterocolitis
Clonazepam	Monotherapy or adjunct therapy in seizure disorders (Lennon-Gastaut, akinetic, absence and myoclonic seizure disorders) Panic disorder with or without agoraphobia
Diazepam	Acute alcohol withdrawal Management of anxiety disorders Muscle spasms Adjunct therapy for seizures Preoperative apprehension and anxiety
Estazolam^	Short-term treatment of insomnia
Flurazepam	Short-term treatment of insomnia
Lorazepam	Management of anxiety disorders Insomnia Premedication for anesthetic procedure Status epilepticus
Midazolam	Management of anxiety disorders Preoperative sedation /amnesia induction Sedation Refractory status epilepticus
Oxazepam	Acute alcohol withdrawal Management of anxiety disorders
Quazepam^	Short-term treatment of insomnia
Temazepam	Short-term treatment of insomnia
Triazolam	Short-term treatment of insomnia

^Currently not covered by Alabama Medicaid

IV. Pharmacokinetics

Table 4. Pharmacokinetics of the Benzodiazepines[1-6, 15-16]

Drug	Alprazolam^	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Estazolam^	Flurazepam
Duration of action	Short	Long	Long	Long	Long	Short	Long
Bioavailability	90%	N/A	90%	91%	98%	N/A	N/A
Protein binding	80%	90-98%	97%	97%-98%	94-99%	93%	97%
Metabolism	Extensively metabolized, primarily by cytochrome P450 3A4 (CYP3A4)	Hepatic; extensively metabolized	Hepatic; extensively metabolized	Hepatic	Hepatic; extensively metabolized	Hepatic; extensively metabolized	Hepatic; extensively metabolized
Active metabolites	Yes; alpha-hydroxy-alprazolam	Yes; desmethyl-chlordiazepoxide and demoxepam	None	Yes; nordiazepam, diazepam and desmethyl-diazepam	Yes; desmethyl-diazepam and nordiazepam	None	Yes; hydroxyethyl-flurazepam and desalkyl-flurazepam
Elimination	Renal	Renal; 1-2% unchanged, 3-6% as conjugate	Renal; <2% unchanged	Renal (62-67%); fecal (15-19%)	Renal (75%)	Renal; fecal (4%)	N/A
Half-Life (h=hours)	6.3-26.9 h	10-48 h	30-40 h	2.3 h (parent compound) 46-48 h (metabolites)	0.83-2.25 days	10-24 h	2.3 h (parent compound) 47-100 h (metabolites)

N/A-= not available

^ Currently not covered by Alabama Medicaid

Table 4. (continued)

Drug	Halazepam	Lorazepam	Midazolam	Oxazepam	Quazepam^	Temazepam	Triazolam
Duration of action	Long	Short	Short	Short	Long	Short	Short
Bioavailability	N/A	90-93%	36%	93%	N/A	N/A	N/A
Protein binding	97%	85-91%	95%	86-99%	95%	96%	89-94%
Metabolism	Hepatic; extensively metabolized	Hepatic; extensively metabolized	Hepatic; extensively metabolized	Hepatic; extensively metabolized	Hepatic; extensively metabolized	Hepatic; extensively metabolized	Hepatic; extensively metabolized
Active metabolites	Yes; desmethyl-diazepam	None	None	None	Yes; oxoquazepam and desalkylflurazepam	Yes; nordiazepam	Yes; alpha-hydroxytriazolam
Elimination	Renal	Renal (88%); fecal (7%)	Renal (45-57%)	Renal	Renal (31%); fecal 23%	Renal (80-90%)	Renal (80%); fecal 9%
Half-Life (h=hours)	14 h	12 h	1.8-6.4 h	2.8-8.6 h	25-41 h (parent compound) 28-84 h (metabolites)	3.5-18.4 h	2.3 h

N/A-= not available
^Currently not covered by Alabama Medicaid

V. Drug Interactions

Table 5. Significant Drug-Drug Interactions with the Benzodiazepines[2-5]

Precipitant Drug	Object Drug	Direction*	Significance Level	Description
Alcohol/CNS depressants (e.g. barbiturates, narcotics)	Benzodiazepines	↑	2	Increased CNS effects (e.g., impaired psychomotor function, sedation) may occur.
Benzodiazepines	Alcohol/CNS depressants (e.g. barbiturates, narcotics)	↑	2	Increased CNS effects (e.g., impaired psychomotor function, sedation) may occur.
Cimetidine Contraceptives, oral Disulfiram Fluoxetine Isoniazid Ketoconazole Metoprolol Propoxyphene Propranolol Valproic acid	Alprazolam Chlordiazepoxide Clorazepate Diazepam Halazepam	↑	2	The elimination of benzodiazepines that undergo oxidative hepatic metabolism (alprazolam, chlordiazepoxide, clorazepate, diazepam, halazepam) may be decreased by the following drugs due to inhibition of hepatic metabolism. Pharmacologic effects of these benzodiazepines may be increased and excessive sedation/impaired psychomotor function may occur.
Diltiazem	Benzodiazepines	↑	2	Diltiazem may decrease the metabolism of certain benzodiazepines and produce prolonged CNS depression.
Grapefruit juice	Benzodiazepines	↑	2	Metabolism of certain benzodiazepines may be inhibited and pharmacologic effects increased.
Macrolides	Triazolam	↑	2	Bioavailability of triazolam will be increased.
Modafinil	Triazolam	↓	2	Metabolism of triazolam may be increased.
Non-nucleoside Reverse Transcriptase Inhibitors	Benzodiazepines	↑	2	Effects of benzodiazepines may be increased and prolonged due to inhibited metabolism.
Protease Inhibitors	Benzodiazepines	↑	2	Effects of benzodiazepines may be increased and prolonged due to inhibited metabolism. Midazolam and triazolam are contraindicated in patients receiving atazanavir.
Rifampin	Benzodiazepines	↓	2	The oxidative metabolism of benzodiazepines may be increased due to microsomal enzyme induction. Pharmacologic effects of some benzodiazepines may be decreased.

Precipitant Drug	Object Drug	Direction*	Significance Level	Description
Benzodiazepines	Phenytoin	↑	2	Phenytoin serum concentrations may be increased, resulting in toxicity, but data are conflicting. Phenytoin may increase oxazepam clearance.

Significance Level 1: Major severity
Significance Level 2: Moderate severity

VI. Adverse Drug Events

Benzodiazepines as a class share a number of adverse drug events. The most common side effects are CNS-related and include sedation, fatigue, ataxia, dizziness, syncope and confusion. Longer acting benzodiazepines or benzodiazepines with active metabolites may have a higher incidence of residual daytime sedation, psychomotor impairment and mental impairment. This may be more pronounced in elderly patients or patients with impaired elimination of benzodiazepines (e.g. hepatic insufficiency). Adverse effects are dose-related and are most pronounced during initiation of therapy. Notable class related adverse drug events and effects are displayed in the table below.

Table 6. Adverse Drug Events Associated with Benzodiazepines[1-6, 17-19]

Body System	Adverse Event
Central nervous system	Amnesia, retrograde: may be more prevalent with short-acting, high potency benzodiazepines (e.g. midazolam, triazolam, lorazepam) Ataxia Behavioral changes: may include confusion, agitation, hyperexcitability, audio/visual hallucinations, paranoid ideation, panic, delirium, and disinhibition Dizziness Fatigue Headache Paradoxical CNS stimulation–excitement, hyperactivity, sleep disturbances, etc. Sedation Seizure: increase frequency in tonic-clonic seizures when used as adjunct for mixed epilepsy. Abrupt discontinuation of benzodiazepine therapy may precipitate withdrawal seizure. Syncope
Gastrointestinal system	Anorexia Constipation Diarrhea Dry mouth Nausea Salivation
Cardiovascular system	Bradycardia–higher risk in severely ill patients Cardiac arrest–higher risk in severely ill patients Hypertension Hypotension–higher risk in severely ill patients Palpitations
Miscellaneous	Changes in libido Dermatologic reactions: urticaria, rash, edema Hypersensitivity reactions Incontinence Menstrual irregularities Respiratory depression (rare) Visual disturbances–diplopia, nystagmus, blurred vision

Dependence[17-18]

Misuse and dependence is a concern associated with benzodiazepine therapy. The risk of dependence increases in the following scenarios:

- Long-term therapy
- High daily dose
- Use of high potency, rapid onset benzodiazepines
- History of substance abuse
- Chronic physical illness
- Chronic sleep disorders
- Dysthymic or personality disorders

Discontinuation Symptoms[17, 19]

Symptoms may occur upon benzodiazepine discontinuation, especially if the therapy is abruptly stopped without a taper period. Symptoms may include relapse of anxiety disorder, rebound symptoms and withdrawal syndromes. Withdrawal symptoms are typically observed only after treatment duration of greater than 4 months, but may be seen in shorter therapies involving high doses. Withdrawal can occur within hours of discontinuation of a short-acting benzodiazepine or as late as 1-2 weeks with long-acting agents. Factors that can predict the severity of discontinuation symptoms include:

- Long-term therapy
- High daily dose
- Short benzodiazepine half-life
- Rapid taper rate
- Concomitant substance abuse

Taper schedules should be individualized to the patient and take into consideration the duration of therapy, concomitant illness, and daily dose.

VII. Dosing and Administration

Table 7. Usual Dosing for the Benzodiazepines[2-6]

	Usual Adult Dose	Usual Pediatric Dose	Availability
Alprazolam^	• Anxiety: immediate release, 0.25-0.5 mg orally 3 times daily; usual dose range is 0.5-4 mg/day (in 2-4 divided doses) • Panic disorder, with or without agoraphobia: immediate release, 0.5 mg orally 3 times daily; may increase dosage by up to 1 mg every 3-4 days. Usual dosage range is 1-10 mg/day (mean, 5-6 mg/day) • Panic disorder, with or without agoraphobia: extended-release, initial, 0.5-1 mg orally in the morning, may increase dosage by up to 1 mg/day every 3-4 days. Usual dosage range is 3-6 mg/day; max 10 mg/day	• Safety and effectiveness in children less than 18 years old have not been established	Oral Concentrate: 1 mg/mL Orally disintegrating tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg Tablet, immediate release: 0.25 mg, 0.5 mg, 1 mg, 2 mg Tablet, sustained release: 0.5 mg, 1 mg, 2 mg, 3 mg
Chlordiazepoxide	• Alcohol withdrawal syndrome: 50-100 mg IM or IV every 2-4 hr as needed to a maximum of 300 mg in 24 hr • Alcohol withdrawal syndrome: 50-100 mg orally initially, to be followed by repeated doses as needed until agitation is controlled; max dose 300 mg/day; dosage then may be reduced to maintenance levels • Anxiety: mild to moderate anxiety; 5 or 10 mg orally 3 to 4 times daily • Anxiety: severe anxiety; 20 or 25 mg orally 3 to 4 times daily • Anxiety: geriatric patients or in the presence of debilitating disease: 5 mg orally 2 to 4 times daily • Anxiety about treatment, Preoperative: 5-10 mg orally 3-4 times a day on days preceding surgery • Anxiety about treatment, Preoperative: 50-100 mg IM one hour prior to surgery	• Anxiety about treatment–Preoperative: (6 yrs and older) 5 mg orally 2 to 4 times daily; may be increased to 10 mg orally 2 to 3 times daily • Anxiety about treatment–Preoperative: initiate therapy with the lowest dose and increase as required	Capsule: 5 mg, 10 mg, 25 mg, Ampule: 100 mg

	Usual Adult Dose	Usual Pediatric Dose	Availability
Clorazepate	• Alcohol withdrawal syndrome: Day 1: initial 30 mg orally, then 30-60 mg orally for the remainder of the day in divided doses • Alcohol withdrawal syndrome: Day 2: 45-90 mg/day orally in divided doses • Alcohol withdrawal syndrome: Day 3: 22.5-45 mg/day orally in divided doses • Alcohol withdrawal syndrome: Day 4: 15-30 mg/day orally in divided doses • Alcohol withdrawal syndrome: Day 5 and after: 7.5-15 mg/day orally in divided doses until the patient's condition is stable • Anxiety: 15-60 mg/day orally in divided doses; usual dose is 30 mg/day (in divided doses) • Epilepsy; Adjunct: initial, 7.5 mg orally 3 times a day • Epilepsy; Adjunct: maintenance, may increase dose by 7.5 mg/wk to a max of 90 mg/day orally (divided doses)	• Epilepsy; Adjunct: children 9-12 yr, initial, 7.5 mg orally 2 times a day • Epilepsy; Adjunct: children 9-12 yr, maintenance, may increase dose by 7.5 mg/wk to a max of 60 mg/day orally (divided doses)	Tablet, immediate release: 3.75 mg, 7.5g, 15 mg Tablet, sustained release: 11.25 mg, 22.5 mg
Clonazepam	• Panic disorder: initial, 0.25 mg orally twice a day for 3 days, then 0.5 mg twice a day • Panic disorder: maintenance, may increase dosage by 0.125-0.25 mg orally twice a day every 3 days to a max total daily dose of 1-4 mg (divided into 2-3 daily doses) • Seizure: initial, 0.5 mg orally 3 times a day • Seizure: maintenance, may increase daily dose by 0.5-1 mg orally every 3 days to a max total daily dose of 20 mg (divided into 3 daily doses)	• Seizure: up to 10 yr of age or up to 30 kg, initial, 0.01-0.03 mg/kg/day orally divided into 2-3 daily doses • Seizure: up to 10 yr of age or up to 30 kg, maintenance, may increase daily dose by 0.25-0.5 mg orally every 3 days to max total daily dose of 0.1-0.2 mg/kg/day (divided into 3 daily doses)	Tablet: 0.5 mg, 1 mg, 2 mg Orally disintegrating tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg
Diazepam	• Alcohol withdrawal syndrome, acute: 10 mg orally 3-4 times a day for 1 day, then 5 mg orally 3-4 times a day as needed • Alcohol withdrawal syndrome, acute: 10 mg IM or IV, then 5-10 mg IM or IV in 3-4 hr if needed • Anxiety: 2-10 mg orally 2-4 times a day • Anxiety: 2-10 mg IM or IV every 3-4 hr if needed • Anxiety: 0.2 mg/kg rectally • Anxiety about treatment–Cardioversion: 5-15 mg IV 5-10min prior to procedure • Anxiety about treatment–Endoscopic procedure: 5-10 mg IM	• Safety and effectiveness not established in children less than 6 months of age • Skeletal muscle spasm–Tetanus: 30 days to 5 yr of age, 1-2 mg IM or IV slowly every 3-4 hr as needed • Skeletal muscle spasm–Tetanus: children 5yr or older, 5-10 mg IM or IV slowly every 3-4 hr as needed • Status epilepticus: children 30 days to 5 yr of age, 0.2-0.5 mg IV slowly (preferred) or IM	Ampule/ disposable syringe/vial: 5 mg/mL Oral solution: 5 mg/5 mL Rectal gel: 2.5 mg, 5 mg, 10, mg 15 mg, 20 mg

	Usual Adult Dose	Usual Pediatric Dose	Availability
	30 min prior to procedure • Anxiety about treatment - Endoscopic procedure: 10 mg or less IV immediately prior to procedure; max dose 20 mg • Seizure; Adjunct: 2-10 mg orally 2-4 times a day • Skeletal muscle spasm: 2-10 mg orally 3-4 times a day • Skeletal muscle spasm: 5-10 mg IM or IV and repeat in 3-4 hr if needed • Status epilepticus: 5-10 mg IV every 10-15 min to a total dose of 30 mg; may repeat in 2 hr if needed	every 2-5 min up to a maximum of 5 mg • Status epilepticus: children 30 days to 5 yr of age, 0.5 mg/kg rectally • Status epilepticus: children 5 yr or older, 1 mg IV slowly (preferred) or IM every 2-5 min up to a maximum of 10 mg; repeat in 2-4 hr if necessary	Tablet: 2 mg, 5 mg, 10 mg
Estazolam^	• Insomnia: 1-2 mg orally at bedtime	• Safety and effectiveness in children less than 18 years old have not been established	Tablet: 1 mg, 2 mg
Flurazepam	• Insomnia: 15-30 mg orally at bedtime	• Safety and efficacy in patients < 15 years old has not been established	Capsule: 15 mg, 30 mg
Lorazepam	• Alcohol withdrawal syndrome: 2 mg orally every 6 hr for 4 doses, then 1 mg every 6 hr for 8 doses • Anxiety: initial, 2-3 mg/day orally divided into 2-3 daily doses • Anxiety: maintenance, 2-6 mg/day orally divided into 2-3 daily doses; max dose 10 mg/day • Insomnia: 2-4 mg orally at bedtime • Nausea and vomiting: A single dose of 0.025-0.05 mg/kg (max 4 mg) IM or IV given slowly (2 mg/min) 30-35 min prior to receiving chemotherapy. This dose may be supplemented with oral lorazepam 1-2 mg/hr as needed • Premedication for anesthetic procedure: 0.05 mg/kg IM (max 4 mg) 2 hr before procedure • Premedication for anesthetic procedure: 0.044 mg/kg IV or 2 mg (whichever is less); max dose 0.05 mg/kg IV or 4mg (whichever is less) • Status epilepticus: 4 mg IV (given slowly, 2 mg/min), may repeat dose in 10-15 min if needed; IM dosing may be used, but IV dosing is preferred	• Safety and effectiveness of lorazepam tablets in children less than 12 years old have not been established • Safety and effectiveness of lorazepam injection in children less than 18 years old have not been established • Status epilepticus: 0.05-0.1 mg/kg IV (max 4 mg/dose)	Ampule/ disposable syringe/vial: 2 mg/mL, 4 mg/mL Oral solution: 2 mg/ml Tablet: 0.5 mg, 1 mg , 2 mg
Midazolam	• Amnesia induction: (< 60 yrs old), 1-2.5mg IV titrated slowly (max infusion rate 1.25 mg/min). Reassess in 2 minutes. A total dose greater than 5 mg is not usually necessary.	• Amnesia induction, loading dose– 0.05-0.2 mg/kg IV over at least 2-3 minutes in intubated patients. Maintenance dose–0.06-	Syringe/Vial: 1 mg/mL, 2 mg/mL, 5 mg/mL

	Usual Adult Dose	Usual Pediatric Dose	Availability
	Maintenance dose is approximately 25%. Patients > 60 yrs old-0.02-0.05 mg/kg IM (approximately 2-3 mg) • Anxiety–Prior to procedures (< 60 yr old): 1-2.5mg IV titrated slowly (max infusion rate 1.25 mg/min). Wait 2 or more minutes to fully evaluate the sedative effect. Reassess in 2 minutes. A total dose greater than 5 mg is not usually necessary. For patients > 60 yrs old, 1-1.5 mg IV titrated slowly (max infusion rate 0.75 mg/min). Reassess in 2 minutes. A total dose greater than 3.5 mg is usually not necessary. Maintenance dose is approximately 25%. • Induction of general anesthesia: 0.3-0.35 mg/kg IV over 20-30 seconds and allowing 2 minutes for effect (max dose 0.6 mg/kg). Increments of approximately 25% of the patient's initial dose may be used if needed to complete induction or induction may instead be completed with inhalational anesthetics • Sedation: loading dose, 0.01-0.05 mg/kg IV (approximately 0.5-4.0mg) may be given slowly or infused over several minutes. May be repeated every 10-15 minutes. Maintenance dose is 0.02-0.10 mg/kg/hr IV (1 to 7 mg/hr). • Status epilepticus, Refractory: 200 mcg/kg IV (via slow bolus injection) initially. Maintenance dose of 0.75-10 mcg/kg/min IV for 12-24 hours	0.12 mg/kg/hr. May increase or decrease by 25% as required. • Anxiety, loading dose: 0.05-0.2 mg/kg IV over at least 2-3 minutes in intubated patients. Maintenance dose: 0.06-0.12 mg/kg/hr. May increase or decrease by 25% as required. • Sedation–For procedures: 0.25-1.0 mg/kg orally given as a single dose (max dose 20 mg) or 0.025-0.05 mg/kg IV over 2-3 minutes. Reassess in 2 minutes. May repeat up to 0.4 mg/kg. Total dose usually does not exceed 10 mg	Syrup: 2 mg/mL
Oxazepam	• Alcohol withdrawal syndrome: 30 mg orally every 6 hr for 4 doses, then 15 mg orally every 6 hr for 8 doses • Anxiety (Mild to Moderate): 10-15 mg orally 3-4 times a day • Anxiety (Severe): 15-30 mg orally 3-4 times a day • Insomnia: 15 mg orally at bedtime	• Safety and efficacy in children under age 6 has not been established and the absolute dose for children ages 6-12 have not been determined	Capsule: 10 mg, 15 mg, 30 mg
Quazepam^	• Insomnia: 15 mg orally at bedtime. Dose can be adjusted to 7.5-30 mg orally at bedtime	• Safety and effectiveness in children less than 18 years old have not been established	Tablet: 7.5 mg, 15 mg
Temazepam	• Insomnia: 7.5-30 mg orally at bedtime	• Safety and effectiveness in children less than 18 years old have not been established	Capsule: 7.5 mg, 15 mg, 30 mg
Triazolam	• Insomnia: initial: 0.25 mg orally at bedtime; max dose 0.5 mg	• Safety and efficacy in children have not been established	Tablet: 0.125 mg, 0.25 mg

^Currently not covered by Alabama Medicaid

VIII. Effectiveness

Table 8. Outcomes Evidence for the Benzodiazepines

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Insomnia						
Holbrook et al.[20]	Meta-analysis (45 randomized trials)	Randomized trials involving patients with insomnia and comparing benzodiazepines against placebo or an active agent	2,672	• Benzodiazepines - Triazolam–16 trials - Flurazepam–14 trials - Temazepam–13 trials - Midazolam–5 trials - Nitrazepam–4 trials - Estazolam–2 trials - Lorazepam, diazepam, brotizolam, quazepam, loprazolam and flunitrazepam–1 trial • Zopiclone*–13 trials • Diphenhydramine, glutethimide, promethazine–1 trial • Cognitive behavioral therapy–1 trial • Placebo –4 trials	Varied (1 day to 6 weeks, mean 12.2 days)	**Benzodiazepines vs. placebo** • Nonsignificant decrease in sleep latency compared to placebo (4.2 minutes) • Significant increase in sleep duration compared to placebo (61.8 minutes) • Significantly high incidence of adverse effects, but no difference observed in dropout rates **Benzodiazepines vs. zopiclone** • No significant difference in sleep latency • Significant increase in sleep duration in benzodiazepine group (Overall difference-23.1 minutes) **Benzodiazepines vs. antihistamines** • No significant difference detected for any sleep outcome **Benzodiazepines vs. behavioral therapy** • Triazolam more effective in reducing sleep latency early in trial, but efficacy decreased by second week of treatment • Behavioral therapy efficacy maintained throughout 9-week follow-up

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Smith et al.[21]	Meta-analysis (21 randomized trials)	Trials involving patients with primary insomnia	470	• Pharmacotherapy - Benzodiazepine receptor agonists–8 trials* • Behavioral treatment–14 trials* • Placebo * one trial directly compared pharmacotherapy and behavioral therapy	Varied	• No differences in total sleep time, number of awakenings, wake time after sleep onset, and sleep quality between benzodiazepine receptor agonists and behavioral therapy • Behavioral therapy group had greater reduction in latency to sleep onset than benzodiazepine receptor agonists (95% CI 0.17-1.04)
Anxiety Disorders						
Mitte et al.[22]	Meta-analysis (48 randomized trials)	Randomized trials involving patients with GAD. Focus on trials comparing benzodiazepines against azapirones	12,053	• Benzodiazepines • Azapirones - Buspirone–12 trials	Not reported (minimum duration for inclusion=14 days)	• No significant differences in efficacy observed between benzodiazepines and azapirones • Significantly less dropouts in benzodiazepine group (20.5% vs 30.7%, $p<0.05$). Reason for dropouts not specified.
Blanco et al.[23]	Meta-analysis (23 randomized trials)	Randomized trials involving patients being treated for social anxiety disorder	2,954	• Benzodiazepines • Antidepressants - SSRI, MAOI, reversible inhibitor of monoamine-oxidase-A (RIMA) • Beta-blockers • Gabapentin • Buspirone	Varied (6-20 weeks)	• Largest effect sizes (effect size): phenelzine (1.02), clonazepam (0.97), gabapentin (0.78), brofaromine (0.66) and SSRI (0.65) • No statistical differences detected between these medications or medication groups • Safety and tolerability evidence supports SSRI as first-line therapy choice. *Note: Effect size is the difference between two population means divided by the standard deviation of either population. Effect sizes of >0.8 are considered large.

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
van Balkom et al.[24]	Meta-analysis (106 trials)	Randomized trials involving patients being treated for panic disorder with or without agoraphobia	5,011	• Benzodiazepines • Antidepressants • Psychological panic management • Exposure in vivo	Varied	• Antidepressants, psychological panic management and antidepressants/exposure in vivo combination demonstrated significant improvement compared to a control condition (placebo, attention placebo and waiting list) in reduction of panic, agoraphobia, depression, and anxiety. • High-potency benzodiazepines showed significant improvement to control condition only in panic, agoraphobia, and anxiety. • No significant differences in treatments for panic disorder. • Antidepressant/exposure in vivo test groups had significant improvements compared to other treatments except exposure in vivo in agoraphobia. • Significantly greater improvement in antidepressant/exposure in vivo compared to exposure in vivo alone and psychological panic management/exposure in vivo in treatment of depression and anxiety.
Alcohol Withdrawal						
Holbrook et al.[25]	Meta-analysis (11 randomized trials)	Randomized trials involving patients being treated for acute alcohol withdrawal	1,286	• Benzodiazepines - Chlordiazepoxide– 5 trials - Diazepam–3 trials - Oxazepam–2 trials - Lorazepam–1 trial	Varied (1-21 days)	• No significant difference in efficacy between individual benzodiazepines • Alternative medications not found to be more beneficial than

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
				• Alternative active treatments - Bromocriptine, carbamazepine, chlorpromazine, clonidine, doxepin, ethanol, paraldehyde, propranolol, thiamine • Placebo		benzodiazepines • No significant difference between benzodiazepines and the alternative treatments in adverse events or dropout rates

***** Not available in US

Additional Evidence

Dose Simplification: A literature search of Medline and Ovid did not reveal clinical studies on dose simplification in relation to the benzodiazepines.

Stable Therapy: A literature search of Medline and Ovid did not reveal clinical studies that have evaluated the effect of changing from one benzodiazepine to another.

Impact on Physician Visits: A literature search of Medline and Ovid did not reveal clinical studies that have evaluated the impact of use of these drugs on physician visits.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this AHFS drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current AL Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the AL Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the AL Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0 - $25 per Rx
$$	$26 -$50 per Rx
$$$	$51-$75 per Rx
$$$$	$76-$100 per Rx
$$$$$	$101-$150 per Rx

Rx = prescription

Table 9. Relative Cost of the Benzodiazepines

Generic Name	Form	Example Brand Name(s)	Brand Cost	Generic Cost
Alprazolam^	Extended-release tablet, oral concentrate, orally disintegrating tablet, tablet	Xanax®*, Niravam®, Xanax XR®	$$$$-$$$$$	$$$
Chlordiazepoxide	Capsule, injection	Librium®*	$$$$	$
Clonazepam	Tablet	Klonopin®*	$$$$	$$$
Clorazepate	Tablet	Tranxene T-Tab®*	$$$$$	$$
Clorazepate	Extended-release tablet	Tranxene SD®	$$$$	N/A
Diazepam	Tablet, injection, solution	Valium®*	$$$$	$
Diazepam	Rectal gel	Diastat®	$$$$$	N/A
Estazolam^	Tablet	Prosom®*	$$	$
Flurazepam	Capsule	Dalmane®*	$$	$
Halazepam‡^	Tablet	Paxipam®	$$$	N/A
Lorazepam	Oral concentrate, injection, tablet	Ativan®*	$$$$	$
Oxazepam	Capsule	Serax®*	$$$$	$$
Quazepam^	Tablet	Doral®	$$$$	N/A

Generic Name	Form	Example Brand Name(s)	Brand Cost	Generic Cost
Temazepam†	Capsule	Restoril®*	$$$	$
Triazolam	Tablet	Halcion®*	$$	$

*Generic is available in at least one dosage form or strength.
† Generic is not available for 7.5 and 22.5 mg strengths.
‡ Product was discontinued by manufacturer.
^Product is currently not covered by Alabama Medicaid.
N/A = not available

X. Conclusions

Benzodiazepines are primarily used for the treatment of anxiety disorders, induction of short-term treatment of insomnia, and as an adjunct therapy for epilepsy. In addition, they are approved for treatment of acute alcohol withdrawal and muscle relaxation. Currently, benzodiazepines may be considered as a first-line therapy option in panic disorders and generalized anxiety disorders where the patient experiences acute anxiety reactions. These guidelines recognize that more clinical evidence supports the use of SSRI antidepressants in anxiety states and that these medications have a greater safety profile.

In regards to treatment of insomnia, all agents within this review are indicated for short-term treatment of insomnia. Currently, there are no guidelines that recommend one particular pharmacological agent as a first -line therapy choice in the treatment of insomnia. Cognitive behavioral therapy is a nonpharmacological treatment option that may be more effective than drug therapy. A meta-analysis conducted by Smith et al. of 21 trials concluded that behavioral therapy is more effective than benzodiazepines in latency to sleep onset and equally effective in total sleep time, number of awakenings, wake time after sleep onset, and sleep quality. Current guidelines for the management of chronic insomnia recommend behavioral therapy as a first-line therapy option and have identified that little evidence supports the use of non-benzodiazepine receptor agonists in the treatment of chronic insomnia.

Benzodiazepines are considered to be first-line therapy options for the management of alcohol withdrawal that is considered moderate-to-severe in nature or in patients with a history of withdrawal seizures or serious comorbid condition. No one benzodiazepine was found to be safer or more efficacious in the relief of symptoms and within the guideline, it is accepted that the benzodiazepines were equally effective.

Benzodiazepines are considered to be a first-line agent in patients experiencing convulsive status epilepticus. In an outpatient scenario where a non-healthcare professional will be administrating the medication with no IV access, the rectal administration of diazepam is the preferred initial intervention. Currently, the only available formulation is Diastat®.[12]

Direct comparison trials within this class are limited and there is insufficient evidence that demonstrates one benzodiazepine is better than another. Diastat® provides a beneficial route of administration over generic agents for its primary indication, status epilepticus. Therefore, with the exception of Diastat®, all other brand products at the doses reviewed are comparable to each other and the generic products in this class and offer no significant clinical advantage over other alternatives in general use.

Currently, Alabama Medicaid does not cover alprazolam, estazolam, halazepam, and quazepam formulations. Alprazolam and estazolam are available generically and there is insufficient evidence to demonstrate that alprazolam or estazolam poses a significant safety risk over other currently covered benzodiazepines.

XI. Recommendations

Diazepam rectal gel (Diastat®) is recommended for preferred status.

Except for diazepam rectal gel, no brand benzodiazepine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics
Miscellaneous Anxiolytics, Sedatives, and Hypnotics AHFS Class 282492
December 14, 2005

I. Overview

Primary insomnia, as defined by *The Diagnostic and Statistical Manual of Mental Disorders,* is difficulty in initiating or maintaining sleep for at least one month, causing marked distress or impairment in social, occupational, or other important areas of functioning. The disturbance of sleep (or associated daytime fatigue) is not due to another sleep disorder such as narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder and parasomnia. A sleep disturbance that occurs exclusively during the course of a mental disorder (e.g. major depressive disorder, generalized anxiety disorder or delirium) or one that is due to a medication, drug of abuse, or general medical condition, is also not considered a diagnosis of primary insomnia.[1] Essentially, a diagnosis of primary insomnia is made after other possible mental and medical disorders have been excluded.

Management of insomnia is most effective when the choice of treatment is patient-specific taking into consideration age, duration of symptoms, severity and etiologies. For many patients, treatment of insomnia with non-pharmacological behavioral changes may be as effective as drug therapy.

Anxiety states are a collection of conditions in which a generalized pervasive fear dominates a patient's life. Anxiety disorders include the following: generalized anxiety disorder, obsessive compulsive disorder, panic disorder, post-traumatic stress, and social phobias.[1]

The AHFS class of miscellaneous anxiolytics, sedatives, and hypnotics includes medications not classified as barbiturates or benzodiazepines that are used primarily for sedation and relief of anxiety disorders. This review encompasses all dosage forms and strengths. (See Table 1.) In accordance with Preferred Drug Legislation, this review does not include information on the hypnotic Rozerem® (ramelteon) because it has not been on the market for at least 6 months. This medication will be reviewed at a future time.

Table 1. Single Entity Miscellaneous Anxiolytics, Sedatives, and Hypnotics in this Review [2-6]

Generic Name	Formulation	Example Brand Name(s)
Buspirone	Tablet	Buspar®*
Chloral hydrate	Capsule, suppository, syrup	Aquachloral®, Noctec®*, Somnote®*
Chlormezanone	Tablet	Trancopal®
Dexmedetomidine^	Injection	Precedex®
Droperidol^	Injection	Inapsine®*
Eszopiclone	Tablet	Lunesta®
Ethchlorvynol	Capsule	Placidyl®
Glutethimide	Tablet	Doriden®†
Hydroxyzine hydrochloride	Injection, syrup, tablet	Atarax®*
Hydroxyzine pamoate	Capsule, suspension	Vistaril®*
Methotrimeprazine	Injection	Levoprome®
Meprobamate	Tablet	Miltown®*
Zaleplon	Capsule	Sonata®
Zolpidem	Tablet	Ambien®
Zolpidem, extended-release	Tablet, extended-release	Ambien® CR

*Generic is available in at least one dosage form or strength.
^Injectable therapy not typically used in an outpatient setting.
†Product is no longer manufactured.

II. Evidence Based Medicine and Current Treatment Guidelines

The following is a brief representation of treatment guidelines containing the miscellaneous anxiolytics, sedatives, and hypnotics.

Table 2. Treatment Guidelines Using the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Clinical Guideline	Recommendation
Standards of Practice Committee of the America Academy of Sleep Medicine: **Nonpharmacologic Treatment of Chronic insomnia**[7]	**Standard–**generally accepted patient-care strategy which reflects a high degree of clinical certainty Stimulus control Training that re-associates the bed and bedroom with rapid sleep onset **Guideline–** patient-care strategy which reflects a moderate degree of clinical certainty Progressive muscle relaxation Method of tensing and relaxing muscles Paradoxical intention Patients attempt to stay awake Biofeedback Visual or auditory feedback to reduce somatic arousal **Option–** patient-care strategy which reflects uncertain clinical certainty Sleep restriction Limit amount time spent in bed to actual time spent asleep Multi-component cognitive behavioral therapy Combined therapies which may include stimulus control, progressive muscle relaxation or sleep restriction as a single therapy
National Institutes of Health (NIH) State-of-the-Science Conference Statement: **Chronic Insomnia in Adults**[8]	**Conference Statement:** "Evidence supports the efficacy of cognitive-behavioral therapy and benzodiazepine receptor agonists in the treatment of this disorder (chronic insomnia), at least in the short term. Very little evidence supports the efficacy of other treatments, despite their widespread use."

Clinical Guideline	Recommendation
Consensus Statement from the International Consensus Group on Depression and Anxiety: **Panic Disorder**[9]	**Acute** **First line:** SSRIs, initiated at low dose. **Second line:** Concomitant use of a benzodiazepine for a limited period (< 8 weeks) may be considered to help initiate treatment with a SSRI. **Maintenance** Limited evidence suggests that once patient is in full remission, the therapeutic dose may be reduced slowly. **Second line (non-responders):** If patient fails to respond at the maximum tolerated dose of a SSRI, or if partial response was observed and the SSRI well tolerated, switch to another SSRI. If SSRI not tolerated, initiate trial with a benzodiazepine or tricyclic antidepressant (TCA). **Third line:** Monoamine oxidase inhibitor (MAOI) or valproate. **Duration of treatment:** 8 to 12 weeks of treatment is considered an adequate trial. If remission is maintained, consider stopping treatment after 12-24 months.
Consensus Statement from the International Consensus Group on Depression and Anxiety: **Generalized Anxiety Disorder (GAD)**[10]	**First line:** Antidepressants–SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs) or least-sedating TCAs. **Second line:** Buspirone **Adjunct therapies:** • Benzodiazepines: consider as first-line therapy agent in an acute anxiety reaction. Use as adjunct agent in acute exacerbations of GAD or sleep disturbances during the initiation of antidepressant therapy. Patient should be stabilized on antidepressant therapy for > 4 weeks before benzodiazepines are slowly tapered (over 4-8 weeks). • Hydroxyzine: consider use in acute anxiety states.
Consensus Statement from the International Consensus Group on Depression and Anxiety: **Social Anxiety Disorder (SAD)**[11]	**Pharmacological treatment recommendation**: SSRI. Most studies conducted with paroxetine. Dose should be initiated at 20 mg/day for 2-4 weeks and then titrated to obtain a response. **Duration of treatment:** Adequate trial of therapy requires 6 to 8 weeks of treatment. If treatment is effective and remission maintained, minimum duration of therapy is 12 months. Note: there is no clinical evidence that benzodiazepines, TCA, or β-blockers as a class are effective for treatment of social anxiety disorder.

III. Indications

Table 3. Comparison of FDA-Approved Indications[2-6, 12-15]

Drug	FDA-approved indications
Buspirone*	Management of anxiety disorders; Short-term relief of symptoms of anxiety
Chloral Hydrate*	Nocturnal sedation; Preoperative sedation; Adjunct to opiates and analgesics; Alcohol withdrawal syndrome
Dexmedetomidine	Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting
Droperidol*	Reduce the incidence of nausea and vomiting in surgical and diagnostic procedures
Eszopiclone	Insomnia
Glutethimide	Short-term treatment of insomnia
Hydroxyzine*	Symptomatic relief of anxiety and tension; Management of pruritus; Sedative before and after general anesthesia; Alcohol withdrawal syndrome; Control nausea and vomiting
Meprobamate*	Management of anxiety disorders
Zaleplon	Short-term treatment of insomnia
Zolpidem	Short-term treatment of insomnia
Zolpidem, extended-release	Insomnia characterized by difficulty with sleep onset and/or sleep maintenance

*Generic available

IV. Pharmacokinetics

Table 4. Pharmacokinetic Parameters of the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[2-6, 12-15]

	Buspirone	Chloral Hydrate	Dexmedetomidine	Droperidol	Eszopiclone
Mechanism of Action	Unknown	Unknown	Selective alpha-2 adrenoceptor agonist	Partial alpha-2 adrenoceptor antagonist, dopamine-2 receptor antagonist, inhibition of chemical trigger zone	Unknown; effects believed to be result of interaction with gamma aminobutyric acid (GABA) at the GABA-A-receptors
Pharmacokinetics					
Bioavailability	90%	nd	73%	nd	nd
Protein binding	86%	35-41%	94%	nd	52-59%
Metabolism	Hepatic (CYP3A4)	Hepatic	Hepatic (CYP2D6)	Hepatic	Hepatic (CYP3A4 and CYP 2E1)
Active Metabolites	Yes; 1-pyrimidinyl piperazine	Yes; trichloroethanol	None	None	Yes; (S)-N-desmethylzopiclone
Elimination	Fecal (18-38%)/ Renal (29-63%)	Biliary/Renal	Fecal (4%)/ Renal (95%)	Fecal (22%)/ Renal (75%)	nd
Half-Life	2-3 hours	7-10 hours	2 hours	2 hours	6 hours

Table 4. (cont.)

	Glutethimide	Hydroxyzine	Meprobamate	Zaleplon	Zolpidem†
Mechanism of Action	Unknown	Unknown; skeletal muscle relaxation, bronchodilator activity, anti-histaminic and analgesic effects have been demonstrated experimentally	Blockade of the long internuncial neuron circuits between the cerebral cortex and the thalamus	Selective binding to the benzodiazepine-1 (omega-1) receptor subtype	Selective binding to the benzodiazepine-1 (omega-1) receptor subtype
Pharmacokinetics					
Bioavailability	nd	nd	nd	30%	70%
Protein Binding	47-59%	nd	15%	60%	93%
Metabolism	nd	Hepatic	Hepatic	Hepatic (aldehyde oxidase and CYP3A4)	Hepatic
Active Metabolites	Yes; 4-OH-glutethimide and 4-hydroxy-2-ethyl-2-phenylglutarimide	Yes; cetirizine	nd	None	None
Elimination	Renal	nd	Fecal (< 10%)/ Renal (90%)	Fecal 17%/ Renal (71%)	Biliary/Renal
Half-Life	12-14 hours	3-20 hours	6-17 hours	1 hour	2.5 hours

nd=no data
†pharmacokinetics for immediate and extended release formulation

V. Drug Interactions

Table 5. Significant Drug-Drug (Level 1 & 2) Interactions with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[2-6, 12-15]

	Object Drug	Effect	Significance Level	Comments
Alcohol	Chloral hydrate Glutethimide Meprobamate	↑	2	Additive depressant effect: Potential disulfiram-like reaction with chloral hydrate: Decrease clearance of meprobamate
Chloral hydrate Dexmedetomidine Droperidol Hydroxyzine Meprobamate Zolpidem	CNS depressants	↑	2	Additive CNS depressant effects
CNS depressants	Chloral hydrate Dexmedetomidine Droperidol Hydroxyzine Meprobamate Zolpidem	↑	2	
CYP3A4 Inducers (e.g. rifamycins, diltiazem)	Buspirone Eszopiclone Zaleplon Zolpidem	↓	2	Potential decrease in object drug levels

	Object Drug	Effect	Significance Level	Comments
CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics)	Buspirone Eszopiclone Zaleplon Zolpidem	↑	2	Potential increase exposure of object drug
Droperidol	Ziprasidone	↑	1	Risk of life-threatening cardiac arrhythmias including Torsades de pointes
Glutethimide	Warfarin	↓	2	Potential for decreased anticoagulant response due to increased metabolism
Parenteral analgesics	Droperidol	↑	2	Reports of hypertension with coadministration of droperidol and parenteral analgesics
Ritonavir	Zolpidem	↑	2	Inhibition of zolpidem metabolism may result in severe sedation and respiratory depression

Significance Level 1: Major severity
Significance Level 2: Moderate severity

VI. Adverse Drug Events

Table 6. Common Adverse Events (%) Reported with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics (> 1%) [2-6, 12-15]

	Buspirone	Dexmed-etomidine	Eszopiclone	Glutethimide	Zaleplon	Zolpidem
GI						
Abdominal Pain	2	—	—	—	5	2
Constipation	—	—	—	—	—	2
Diarrhea	—	—	—	—	—	3
Dry Mouth	3	—	7	—	—	3
Dyspepsia	—	—	5	—	4	5
Nausea	8	11	4	3	7	6
Vomiting	—	4	3	—	—	—
Cardiovascular						
Arrhythmia	—	4	—	—	—	—
Bradycardia	—	7	—	—	—	—
Hypertension	—	16	—	—	—	—
Hypotension	—	28	—	—	—	—
Tachycardia	—	3	—	—	—	—
CNS						
Agitation	2	—	—	—	—	—
Amnesia	—	—	—	—	4	—
Anxiety	—	—	3	—	—	—
Arthralgia	—	—	—	—	—	4
Confusion	2	—	—	—	—	—
Depression	2	—	4	—	—	2
Dizziness	12	—	7	—	7	5
Hallucination	—	—	3	—	—	—
Headache	6	—	17	—	28	19
Insomnia	3	—	—	—	—	—
Lightheadedness	3	—	—	—	—	—
Nervousness	5	—	5	—	—	—
Paresthesia	—	—	—	—	3	—
Somnolence	10	—	10	—	5	8
Tremor	—	—	—	—	2	—
Metabolic						
Acidosis	—	2	—	—	—	—
Hyperglycemia	—	2	—	—	—	—
Respiratory						
Apnea	—	—	—	—	—	—
Hypoxia	—	4	—	—	—	—
Infection	—	—	10	—	—	5
Miscellaneous						
Allergy	—	—	—	—	—	4
Anemia	—	3	—	—	—	—
Fatigue	4	—	—	—	—	—
Fever	—	5	—	—	2	—
Hemorrhage	—	3	—	—		—
Myalgia	—	—	—	—	7	7
Oliguria	—	2	—	—	—	—
Pain (non-specific)	—	2	—	—	—	—
Rash	—	—	4	—	—	2
Thirst	—	2		—	—	—

	Buspirone	Dexmed-etomidine	Eszopiclone	Glutethimide	Zaleplon	Zolpidem
Unpleasant Taste	—	—	34	—	—	—
Viral Infection	—	—	3	—	—	—
Visual Disturbances	—	—	—	—	—	—
Weakness	—	—	—	—	8	—

The following adverse reactions occurred at an unknown incidence:

Chloral Hydrate:
Somnambulism, disorientation, incoherence, paranoid behavior, excitement, delirium, drowsiness, staggering gait, ataxia, vertigo, nightmares, malaise, mental confusion, headache, hallucinations, skin rashes, nausea and vomiting, flatulence, diarrhea, taste disturbances, leucopenia, eosinophilia, hangover, ketonuria, idiosyncratic syndrome.

Droperidol:
QT interval prolongation, Torsade de pointes, cardiac arrest, ventricular tachycardia, hypotension, tachycardia, dysphoria, drowsiness, restlessness, hyperactivity, anxiety, extrapyramidal symptoms (dystonia, akathisia, oculogyric crisis), anaphylaxis, dizziness, chills, laryngospasms, bronchospasms.

Hydroxyzine:
Dry mouth, drowsiness, involuntary motor activity, tremor, convulsion, hypersensitivity reactions.

Meprobamate:
Palpitations, tachycardia, arrhythmias, transient ECG changes, syncope, hypotensive crises, drowsiness, ataxia, dizziness, slurred speech, headache, vertigo, weakness, visual disturbances, euphoria, paradoxical excitement, over stimulation, nausea, vomiting, diarrhea, allergy, rash, hyperpyrexia, chills, angioneurotic edema, bronchospasms, Steven-Johnson syndrome, agranulocytosis, aplastic anemia, thrombocytopenia purpura.

VII. Dosing and Administration

Table 7. Usual Dosing for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[2-6, 12-15]

	DEA schedule	Usual Adult Dose	Usual Pediatric Dose	Availability
Buspirone	Rx	Anxiety: 5 mg 2-3 times a day or 7.5 mg twice a day May increase by 5 mg/day every 2-3 days as needed (usual dose 20-30 mg/day in 2-3 divided doses, max dose 60 mg/day	Safety and efficacy in patients < 18 years old has not been established	Tablet: 5 mg, 7.5 mg, 10 mg, 15 mg, 30 mg
Chloral hydrate	IV	Alcohol withdrawal syndrome: 500 mg-1 g every 6 hr Insomnia: 500 mg-1 g orally or rectally 15-30 min before bedtime (max dose 2 g/day) Postoperative pain: Adjunct: 250 mg orally or rectally 3 times a day after meals (max dose 2 g/day) Preoperative sedation: 500 mg-1 g 30 min before surgery (max dose 2 g/day) Sedation: 250 mg orally or rectally 3 times a day after meals (max dose 2 g/day)	Conscious sedation: 25-120 mg/kg orally or rectally (max single dose is 2 g) Insomnia: 50 mg/kg/day OR 1.5 g/m(2) orally or rectally (max 1 g per single dose) Premedication for procedure: 25-100 mg/kg (max 1 g per single dose, max total dose 100 mg/kg or 2 g)	Capsule: 500 mg Suppository: 324 mg, 500 mg, 648 mg Syrup: 500 mg/5 mL
Dexmedetomidine	Rx	Loading infusion: 1 mcg/kg over 10 minutes Maintenance: 0.2-0.7 mcg/kg/hr Max duration of infusion=24 hrs	Safety and efficacy in patients < 18 years old has not been established	Vial: 200 mcg/2mL
Droperidol	Rx	Initial: 2.5 mg IM or slow IV Additional 1.25 mg doses may be given to achieve desired effect	(Ages 2-12 yrs): 0.1 mg/kg	Ampule/vial: 2.5 mg/mL

	DEA schedule	Usual Adult Dose	Usual Pediatric Dose	Availability
Eszopiclone	IV	Initial: 2 mg immediately before bedtime Dose may be increased to 3 mg Elderly initial: 1 mg immediately before bedtime if main complaint is difficulty falling asleep 2 mg immediately before bedtime if main complaint is difficulty staying asleep Dose may be increased to 2 mg	Safety and efficacy in patients < 18 years old has not been established	Tablet: 1 mg, 2 mg, 3 mg
Glutethimide	II	250-500 mg at bedtime	Safety and efficacy in patients < 18 years old has not been established	Tablet: 500 mg
Hydroxyzine HCl/ Hydroxyzine pamoate	Rx	Adjunct – Postoperative care: 50-100 mg or 25-100 mg IM (HCl only) Alcohol withdrawal syndrome (HCl only):50-100 mg IM immediately, then every 4-6 hrs as needed Anxiety: 50-100 mg orally four times daily Premedication for procedure; Adjunct: 50-100 mg orally or 25-100 mg IM (HCl only) Pruritus: 25 mg orally 3-4 times daily Vomiting (HCl only):: excluding nausea and vomiting of pregnancy, 25-100 mg IM	Adjunct – Postoperative care: 0.6 mg/kg orally or 1.1 mg/kg of body weight IM (HCl only): Anxiety: (over 6 yrs) 50-100 mg/day orally in divided doses Anxiety: (under 6 yrs) 50 mg/day orally in divided doses Premedication for procedure; Adjunct: 0.6 mg/kg orally or 1.1 mg/kg of body weight IM (HCl only) Pruritus: (over 6 yrs) 50-100 mg/day orally in divided doses Pruritus: (under 6 yrs) 50 mg/day orally in divided doses Vomiting: 1.1 mg/kg of body weight IM (HCl only)	Hydroxyzine HCl: Syrup: 10 mg/5 mL Tablet: 10 mg, 25 mg, 50 mg Vial: 25 mg/mL, 50 mg/mL Hydroxyzine pamoate: Capsule: 25 mg, 50 mg, 100 mg Suspension: 25 mg/5 mL

	DEA schedule	Usual Adult Dose	Usual Pediatric Dose	Availability
Meprobamate	IV	1200-1600 mg/day orally (3-4 divided doses); max dose 2400 mg/day	(Ages >6 yrs): 200-600 mg/day orally (2-3 divided doses)	Tablet: 200 mg, 400 mg
Zaleplon	IV	10 mg at bedtime; max dose 20 mg	Safety and efficacy in patients < 18 years old has not been established	Capsule: 5 mg, 10 mg
Zolpidem	IV	Immediate-release: 10 mg at bedtime 5 mg at bedtime for elderly, debilitated or patients with hepatic deficiency Extended-release: 12.5 mg at bedtime 6.25 mg at bedtime for elderly, debilitated or patients with hepatic deficiency	Safety and efficacy in patients < 18 years old has not been established	Tablet (immediate-release): 5 mg, 10 mg Tablet (extended-release): 6.25 mg, 12.5 mg

VIII. Effectiveness

Table 8. Comparative Trials with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Llorca et al.[16]	Randomized, double-blind, placebo-controlled trial	• Adults w/ GAD • Hamilton Anxiety Rating > 20	334	• Hydroxyzine 50 mg/day (12.5 mg in AM and noon, 25 mg PM) n=105 • Bromazepam* 6 mg/day (1.5 mg in AM and noon, 3 mg in PM) n=116 • Placebo n=113	12 weeks	Improvement in Hamilton Anxiety Rating Scale (HAM-A) after 12 weeks: • Hydroxyzine–12.16 ($p<0.02$ vs placebo) • Bromazepam–not reported, but reported as significant vs placebo Significantly higher number of responders (> 50% reduction in HAM-A) in hydroxyzine and bromazepam groups

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
						Differences between hydroxyzine and bromazepam* were not significant
Lader et al.[17]	Randomized, double-blind, placebo-controlled trial	• Adults w/ GAD • Hamilton Anxiety Rating > 20	244	• Hydroxyzine 50 mg/day (12.5 mg in AM and noon, 25 mg in PM) n=81 • Buspirone 20 mg/day (5 mg in AM and noon, 10 mg in PM) n=82 • Placebo n=81	4 weeks	Improvement in Hamilton Anxiety Rating Scale (HAM-A) after 4 weeks: • Hydroxyzine–10.8 (p<0.02 vs placebo) • Buspirone–8.8 (p=ns vs placebo) • Difference between hydroxyzine and buspirone not significant
Gammans et al.[18]	Metanalysis (8 randomized, controlled trials)	• Adults w/ GAD • Hamilton Anxiety Rating > 18	509	• Buspirone (doses varied, max=60 mg/day) n=264 • Placebo n=245	Varied	Improvement in Hamilton Anxiety Rating Scale (HAM-A) (pooled results): • Buspirone–11.1 (p<0.001 vs placebo) Patients with GAD with concurrent depressive symptoms demonstrated significant improvement over placebo (p≤ 0.05)
Fillingim et al.[19]	Randomized, double-blind, placebo-controlled trial	• Adults w/ chronic or sporadic insomnia	75	• Temazepam 30 mg at HS n=25 • Glutethimide 500 mg at HS n=25 • Placebo n=25	4 days	• Study subject questionnaires showed significant improvement (p< 0.05) in sleep induction, sleep induction time, nocturnal awakenings, early morning awakenings, duration of sleep and quality of sleep observed in temazepam and glutethimide group vs placebo • No difference measured between temazepam and glutethimide group

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Piccione et al.[20]	Double-blind, cross-over trial	• Elderly (> 60 yrs) patients with insomnia	27	• Chloral hydrate 250 and 500 mg • Triazolam 0.25 and 0.5 mg • Placebo Participants received each of the 5 treatments on 5 consecutive nights	5 days	Efficacy based on subjective measure on 5 point scale (0=poor sleep, 5=good sleep) • Triazolam 0.25 mg - significantly better than placebo in sleep latency and total sleep time ($p< 0.05$) - significantly better than chloral hydrate 250 mg and 500 mg in sleep duration ($p< 0.05$) • Triazolam 0.5 mg - significantly better than placebo in sleep latency and number of awakenings ($p< 0.05$) - significantly better than chloral hydrate 250 mg and 500 mg in global evaluation of medication, sleep latency, number of awakenings and total sleep time ($p<0.05$) • Chloral hydrate - no significant difference observed vs placebo
Elie et al.[21]	Randomized, double-blind, placebo-controlled trial	• Adults with primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorder	615	• Zaleplon 5, 10 or 20 mg n=122, 121,124 (respectively) • Zolpidem 10 mg n=122 • Placebo n=126	4 weeks	• Significant reduction in median sleep latency with zaleplon and zolpidem compared to placebo ($p< 0.05$) • Zaleplon 20 mg and zolpidem significantly increased total sleep time ($p<0.05$) • Subjective sleep scores significantly better in zolpidem group compare to placebo

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
						(p<0.05) • Significantly higher number of zolpidem subjects reported > 3 withdrawal symptoms than placebo Note–Study did not report any direct comparisons between zaleplon or zolpidem groups
Roth et al.[22]	Randomized, double-blind, placebo-controlled trial	• Healthy adults	462	• Zolpidem 5, 7.5, 10, 15, 20 mg n=52, 102,104, 51, 51 (respectively) • Placebo n=102	Single dose	• Significant reductions in latency to persistent sleep, increased sleep duration and increased sleep maintenance in zolpidem 7.5 and 10 mg compared to placebo (p<0.05) • No significant effect on next-day psychomotor performance • Significantly less rapid eye movement (REM) sleep in zolpidem groups than placebo Note–Study focused on zolpidem 7.5 and 10 mg. Pair wise comparison restricted to placebo and these 2 groups
Scharf et al.[23]	Randomized, double-blind, placebo-controlled trial	• Adults with chronic insomnia	75	• Zolpidem 10 mg n=26 • Zolpidem 15 mg n=25 • Placebo n=24	5 weeks	Weeks 1-4 • Significant reductions in latency to persistent sleep and sleep efficiency in both zolpidem groups compared to placebo (p <0.05) Weeks 1-5 • Significant reductions in latency to persistent sleep and sleep efficiency in zolpidem 15 mg

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
						compared to placebo ($p < 0.05$) Subjective evaluations • Subjective sleep latency significantly shorter in zolpidem 15 mg group compared to placebo ($p<0.05$) Zolpidem 10 mg vs 15 mg (subjective evaluation) • Significantly greater ease in falling asleep in 15 mg group in weeks 1,4 and 5 only ($p<0.05$) • Significantly greater quality of sleep reported in 15 mg in first week only ($p<0.05$) • Significantly less morning sleepiness in 10 mg group at week 3 only ($p<0.05$)
Krystal et al.[24]	Randomized, double-blind, placebo-controlled trial	• Adults with chronic insomnia	788	• Eszopiclone 3 mg n=593 • Placebo n=195	6 months	• Significant improvements in sleep induction, sleep maintenance and sleep duration in eszopiclone group over placebo ($p<0.05$) • Subjective ratings on next-day function, alertness and well being significantly better in eszopiclone ($p< 0.05$)

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Zammit et al.[25]	Randomized, double-blind, placebo-controlled trial	• Adults with chronic insomnia	308	• Eszopiclone 2 mg n=104 • Eszopiclone 3 mg n=105 • Placebo n=99	6 weeks	• Significant improvements in sleep onset, sleep maintenance, sleep duration, sleep efficiency, depth of sleep and sleep quality in eszopiclone 3 mg group over placebo ($p<0.05$) • Significant improvements in sleep onset, sleep duration, sleep efficiency, depth of sleep and sleep quality in eszopiclone 2 mg group over placebo ($p<0.05$)

ns-not significant; hs=bedtime
***** Not available in US

Additional Evidence

Dose Simplification: The agents indicated to treat insomnia can all be administered as a single dose at bedtime. Agents within this review that are indicated to treat anxiety require more frequent administration. A literature search of Medline and Ovid did not reveal clinical studies on dose simplification in relation to the miscellaneous anxiolytics, sedatives and hypnotics.

Stable Therapy: A literature search of Medline and Ovid did not reveal clinical studies that have evaluated the effect of changing from within this class to another agent.

Impact on Physician Visits: A literature search of Medline and Ovid did not reveal clinical studies that have evaluated the impact of use of these drugs on physician visits.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this AHFS drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current AL Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the AL Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the AL Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0 - $25 per Rx
$$	$26 -$50 per Rx
$$$	$51-$75 per Rx
$$$$	$76-$100 per Rx
$$$$$	$101-$150 per Rx

Rx = prescription

Table 9. Relative Cost of Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Generic Name	Form	Example Brand Name(s)	Brand Cost	Generic Cost
Buspirone	Tablet	Buspar®*	$$$$	$$
Chloral hydrate	Capsule, syrup, suppository	Aquachloral®, Somnote®*, Noctec®*	$$$	$
Dexmedetomidine^	Injection	Precedex®	$$	N/A
Droperidol^	Injection	Inapsine®*	$	$
Eszopiclone	Tablet	Lunesta®	$$$	N/A
Hydroxyzine hydrochloride	Injection, syrup, tablet	Atarax®*	$$$	$
Hydroxyzine pamoate	Capsule, suspension	Vistaril®*	$$	$
Meprobamate	Tablet	Miltown®*	$$$$$	$$$
Zaleplon	Capsule	Sonata®	$$$$	N/A
Zolpidem	Tablet	Ambien®	$$$	N/A
Zolpidem, extended-release	Extended-release tablet	Ambien CR®	$$$	N/A

*Generic is available in at least one dosage form or strength.
^Injectable therapy not typically used in an outpatient setting.
†Product is no longer manufactured.
N/A = not available

X. Conclusions

The miscellaneous anxiolytic, sedative, and hypnotic medications are primarily used for the treatment of anxiety disorders, induction of sedation and treatment of insomnia. Currently, none of these agents are considered to be first-line for any of the anxiety disorders, primarily due to questions of their tolerability and safety. In addition, these guidelines recognize that more clinical evidence supports the use of SSRI antidepressants in anxiety states and that these medications are generally better tolerated.

In regards to treatment of insomnia, with the exception of eszopiclone, all agents within this review are indicated for short-term treatment of insomnia. Currently, there are no guidelines that recommend one particular pharmacological agent as a first line therapy choice in treatment of insomnia.

Current guidelines for management of chronic insomnia recommend behavioral therapy as a first line therapy option and have identified that little evidence supports the use of non-benzodiazepine receptor agonists in the treatment of chronic insomnia. A meta-analysis conducted by Smith et al. supports this recommendation. A review of 21 trials concluded that behavioral therapy is more effective than benzodiazepines in latency to sleep onset and equally effective in total sleep time, number of awakenings, wake time after sleep onset, and sleep quality.[26]

Direct comparison trials within this class are limited and there is insufficient evidence that demonstrates that any agent is safer or more effective than another. Therefore, all brand products at the doses reviewed are comparable to each other and the generic products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous anxiolytic, sedative, or hypnotic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cerebral Stimulants/Agents used for ADD/ADHD
AHFS Class 282004 and Atomoxetine (AHFS Class 289200)
December 14, 2005

I. Overview

Attention Deficit Hyperactivity Disorder (ADHD) is a severe, debilitating condition that can affect both children and adults. A recent epidemiologic survey reported the prevalence of ADHD in American children at 6.3%,[1] but other sources report the prevalence as high as 12% in school age children, with 60 to 80% of patients continuing to suffer into adolescence or adulthood.[2] ADHD is often characterized by excessive, long-term and developmentally inappropriate impulsivity, attention deficit and in some cases hyperactivity. Untreated or under-treated ADHD is associated with adverse sequelae that include delinquent behavior, antisocial personality traits, substance abuse, and other comorbidities.[3] Suboptimal academic performance is often the impetus for initial screening, diagnosis, and subsequent drug therapy.

The stimulant medications were introduced for the treatment of children with inattention and hyperactivity 65 years ago.[4] Historically, the most widely used medications for ADHD have been methylphenidate and amphetamines. Pemoline has also been used in the treatment of ADHD; however, due to the risk of potential life threatening liver failure, the FDA rescinded its approval on October 24, 2005.

This review will include cerebral stimulants used for ADD/ADHD, and atomoxetine, a non-stimulant medication approved for the treatment of ADHD. Lastly, this review will include modafinil which is a cerebral stimulant that is structurally and pharmacologically distinct from other agents in this class. This medication is indicated for the treatment of narcolepsy, obstructive sleep apnea (OSA) and shift work sleep disorder (SWSD).[5] This review encompasses all dosage forms and strengths.

Table 1. Medications Included in this Review[5,6]

Generic Name	Formulation	Example Brand Name(s)
Cerebral Stimulants		
Amphetamine salts (mixed) (amphetamine/dextroamphetamine)	Tablets Extended-release capsules	Adderall®* Adderall XR®
Dexmethylphenidate	Tablets Extended-release capsules	Focalin® Focalin XR®
Dextroamphetamine	Tablets Extended-release capsules	Dexedrine®*, Dextrostat®* Dexedrine Spansule®
Methamphetamine^	Tablets	Desoxyn®
Methylphenidate	Tablets, chew tablets Solution Extended-release tablets Extended-release capsules	Methylin®*, Ritalin®* Concerta®, Metadate ER®*, Methylin®ER*, Ritalin SR®* Metadate CD®, Ritalin LA®
Modafinil	Tablets	Provigil®
Pemoline	Tablets	Cylert®*
Miscellaneous		
Atomoxetine	Capsules	Strattera®

* Generic is available in at least one dosage form or strength.
^Generic form was available at one time but was recalled by the manufacturer

Cerebral Stimulants can be further divided according to duration of action. The individual differences are listed below.

Table 2. Cerebral Stimulants Classified According to Duration of Action

Medication	Short Acting	Intermediate Acting	Long Acting
Amphetamine products	Dexedrine®, Dextrostat® Duration: 4-6 hours	Adderall®, Dexedrine Spansule®, Duration: 6-8 hours	Adderall XR® Duration: 10-12
Methylphenidate products	Ritalin®, Methylin®, Focalin® Duration: 3-5 hours	Ritalin SR®, Metadate ER®, Methylin ER® Duration: 3-8 hours	Concerta®, Focalin XR®, Metadate CD®, Ritalin LA® Duration: 8-12 hours

II. Evidence Based Medicine and Current Treatment Guidelines

ADHD

Mixed Amphetamine Salts and Methylphenidate
Mixed amphetamine salts and methylphenidate are central nervous system stimulants; although the mechanism of action for ADHD treatment has not been fully elucidated, several theories have been proposed. The cerebral stimulants, in varying degrees, inhibit the reuptake of dopamine and norepinephrine; enhance the release of these biogenic amines from the presynaptic neuron; or inhibit the enzyme monoamine oxidase (MAO).[5] The resultant pharmacologic actions of amphetamines are similar to those of ephedrine and include central nervous system (CNS) and respiratory stimulation and increased sympathomimetic activity. Because the cerebral stimulants possess slightly different mechanisms of action, lack of response to a particular agent is not predictive of response to another.

There are two evidence-based clinical practice guidelines that outline the pharmacological treatment of ADHD: (1) The American Academy of Child and Adolescent Psychiatry: 2002[3], and (2) The American Academy of Pediatrics (AAP) Committee on Quality Improvement: 2001[2]. There is little difference between the two documents. The American Academy of Pediatrics guideline was reviewed by a subcommittee composed of primary care and developmental-behavioral pediatricians and other experts in

the fields of neurology, psychology, child psychiatry, education, family practice, and epidemiology. The subcommittee also partnered with the evidence based practice center at McMaster University to develop the evidence base of literature regarding ADHD. The resulting systematic review, along with other major studies in this area, was used to formulate recommendations for treatment of children with ADHD.

Summary of the AAP Evidence Based Guideline (2001) [2]

Once the diagnosis of ADHD is confirmed, and an interdisciplinary plan of action is established, the clinician should recommend stimulant medication and/or behavior therapy as appropriate to improve outcomes in children with ADHD. When drug and non-drug therapy have not met target outcomes, clinicians should evaluate the original diagnosis, use of all appropriate treatments, adherence to the treatment plan, and presence of coexisting conditions. Since the core symptoms of ADHD (i.e., inattention, impulsivity, hyperactivity) result in multiple areas of dysfunction relating to a child's performance at home, school, and in the community, the primary goal of treatment is to maximize function. Desired results include:

- Improvements in relationships with parents, siblings, teachers, and peers
- Decreased disruptive behaviors
- Improved academic performance, particularly in volume of work, efficiency, completion, and accuracy
- Increased independence in self-care or homework
- Improved self-esteem
- Enhanced safety in the community, such as in crossing streets or riding bicycles

Target outcomes should follow from the key symptoms the child manifests and the specific impairments these symptoms cause. For most children, stimulant medication is highly effective in the management of the core symptoms of ADHD. For many children, behavioral interventions are valuable as primary treatment or as an adjunct in the management of ADHD, based on the nature of coexisting conditions, specific target outcomes, and family circumstances.

Many studies have documented the efficacy of stimulants in reducing the core symptoms of ADHD. In many cases, stimulant medication also improves the child's ability to follow rules and decreases emotional over-reactivity, thereby leading to improved relationships with peers and parents. Most studies of stimulants have been short-term, demonstrating efficacy over several days or weeks. However, the Multimodal Treatment Study (MTA) demonstrated efficacy up to 14 months.[7] This study included 579 children from 7 to 9.9 years of age with ADHD who were randomized to 4 treatment groups: medication management alone, medication and behavior management, behavior management alone, and a standard community care group. The medication management groups followed specific protocols and algorithms relative to routine community practice based on clinicians' best judgments. School-aged children with ADHD showed a marked reduction in core ADHD symptoms over a 14-month period when they were treated with medication management alone or a combination of medication and behavior management. Eighty-five percent of the children treated with medication received a stimulant medication. Despite the efficacy of stimulant medications in improving behaviors, many children who receive them do not demonstrate fully normal behavior (i.e., only 38% of medically managed children in the MTA study received scores in the normal range at 1-year follow-up). Although the MTA study demonstrated that the efficacy of stimulants lasts at least 14 months, the long- term effects of stimulants remain unclear, attributable in part to the lack of additional long-term data.[2]

Stimulant medications currently available include short-, intermediate-, and long-acting methylphenidate, and short-, intermediate-, and long-acting amphetamines. The intermediate- and long-acting amphetamines are mixed salts (75% dextroamphetamine and 25% levoamphetamine). The McMaster report reviewed 22 studies and showed no differences comparing methylphenidate with dextroamphetamine or among different forms of these stimulants. Each stimulant improved core symptoms equally. Individual children, however, may respond to one of the stimulants but not to another.[2]

At least 80% of children will respond to one of the stimulants.[2] Children who fail to show positive effects or who experience intolerable side effects on one stimulant medication should be tried on another of the recommended stimulant medications. The reasons for this recommendation include the following:[2]

- Most children who fail to respond to one medication will have a positive response to an alternative stimulant.
- Safety and efficacy of stimulants in the treatment of ADHD compared with nonstimulant medications has not been established.
- Numerous crossover trials indicate efficacy of different stimulants in the same child.
- Idiosyncratic response to one medication does not dictate a similar response to another.

Children who fail 2 stimulant medications can be tried on a third stimulant medication for the same reason. When the selected regimen has not met targeted outcomes, clinicians should evaluate the original diagnosis, use of all appropriate treatments, adherence to the treatment plan, and presence of coexisting conditions. The clinician should periodically provide a systematic follow-up for the child with ADHD.

Atomoxetine

The aforementioned guidelines do not address atomoxetine as this medication was introduced after the clinical practice guidelines were in print. Atomoxetine is the only non-stimulant medication FDA-approved for the treatment of ADHD. This agent is a neurologic agent with a structure similar to fluoxetine. It is a selective norepinephrine reuptake inhibitor (SNRI).[5] The selective neuronal norepinephrine reuptake inhibition in the brain causes a corresponding increase in norepinephrine in the prefrontal cortex that increases attention and memory. Over time, a resultant desensitization of beta adrenoreceptors occurs. Thus, the efficacy of atomoxetine is not seen immediately. In fact, three to eight weeks of therapy may be necessary before full therapeutic effects are seen.[5] There is minimal to no activity on serotonin or dopamine receptors.

Narcolepsy

The treatment guidelines for narcolepsy are included in the review in order to allow for a comprehensive review of the cerebral stimulant class and address the clinical utility of modafinil. Modafinil is FDA-approved for narcolepsy, as an adjunct for obstructive sleep apnea (OSA), and for shift work sleep disorder (SWSD).[5,6] As with ADHD, amphetamines and methylphenidate are the mainstay of treatment for narcolepsy based on a long record of clinical experience.[7] In spite of this, most clinical trials have involved small numbers of patients, and the risk-to-benefit ratio remains to be established. In addition, there are no head to head trials comparing modafinil to conventional therapies at this time.

Narcolepsy rarely occurs in children, and the relative safety and efficacy of various stimulant drugs in this age group is unclear.[8] Although amphetamines can be used, methylphenidate appears to be used most commonly, based principally on extensive experience with the drug in pediatric patients with ADHD. The treatment of narcolepsy is outlined in a clinical guideline from The American Academy of Sleep Medicine (AASM) 2000. A summary of the recommendations pertaining to pharmacological treatment is outlined in Table 3.

Table 3. AASM Recommendations for the Treatment of Narcolepsy[8]

AASM: Practice Parameters for the Treatment of Narcolepsy: An Update for 2000
• Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for the treatment of daytime sleepiness due to narcolepsy. These medications are the mainstay of narcolepsy treatment. Based on a long history in clinical practice, they have a lengthy record of efficacy. However, the benefit-to-risk ratio is not well documented, because the published clinical trials include only small numbers of patients. • Modafinil is effective for treatment of daytime sleepiness due to narcolepsy. This conclusion is based on the favorable benefit-to-risk ratio for modafinil established in three clinical studies with confirmation from additional studies. • Pemoline is effective for treatment of daytime sleepiness in narcolepsy; however, pemoline can produce rare and potentially lethal liver toxicity that may be unpredictable. Because of this toxicity, the use of pemoline in patients with narcolepsy is rarely indicated. • Combinations of long- and short-acting forms of stimulants may be effective for some patients. Some stimulants are short acting (3 to 4 hours) (i.e. methylphenidate). Others have longer duration of activity and longer onset of action (i.e. modafinil, extended-release amphetamine). By combining stimulants with different activity characteristics, it may be possible to achieve alertness quickly and for longer periods of time and also not produce insomnia as an unwanted side effect. • Combinations of stimulants and antidepressants may be beneficial for the treatment of sleepiness and REM-related symptoms such as cataplexy. For example, modafinil appears compatible with antidepressant medications, but published evidence is limited. • Of the stimulants used to treat narcolepsy, amphetamines, especially at high doses, are the most likely to result in the development of tolerance.

III. Indications

Table 4. FDA-Approved Indications for Cerebral Stimulants and Atomoxetine[5,6,9]

Cerebral Stimulants	Example(s) of Brand Name	ADHD < 6 yo	ADHD ≥ 6 yo	Narcolepsy	OSA*	Other
Mixed Amphetamine Salts	Adderall®	□	□	□		
	Adderall XR®		□			
Dextroamphetamine	Dexedrine® Dextrostat®	□	□	□		Endogenous obesity
Dexmethylphenidate	Focalin® ,Focalin XR®		□			
Methamphetamine	Desoxyn®		□			
Methylphenidate	Ritalin®,Metadate ER®		□	□		
	Ritalin LA®, Metadate CD®, Concerta®		□			
Modafinil	Provigil®			□	□	□ (SWSD)*
Pemoline	Cylert®		□			
Miscellaneous						
Atomoxetine	Strattera®		□			

*OSA= Obstructive Sleep Apnea *SWSD = shift work sleep disorder

Contraindications for Amphetamines:[5,6,9]
Patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, or glaucoma cannot take amphetamines. In addition, patients with psychologically agitated states, or a history of drug abuse, should not take amphetamines. During or within 14 days following the administration of monoamine oxidase inhibitors (MAOI), amphetamines are contraindicated due to the potential for hypertensive crisis.[13]

FDA Alerts for Amphetamines: [5,6,9]
Adderall XR® was removed from the market in Canada in February 2005 due to reports of sudden death in children. This decision was a result of 20 international reports of sudden death in patients taking either Adderall® or Adderall XR® (Adderall®- immediate release was not marketed in Canada). This decision was rescinded in August 2005, however, with modifications to the medication label. FDA review of the reports of sudden deaths in children resulted in the following statement: "SUD (sudden unexplained death) has been associated with amphetamine use and reported in children with underlying cardiac abnormalities taking recommended doses of amphetamines, including Adderall® and Adderall XR®. In addition, a very small number of cases of SUD have been reported in children without structural cardiac abnormalities taking Adderall®. At this time, the FDA cannot conclude that recommended doses of Adderall® can cause SUD, but is continuing to carefully evaluate the data."[10]

Contraindications for Methylphenidate: [5,6,9]
Patients with anxiety and agitation are not candidates for methylphenidate therapy, nor are patients with glaucoma, motor tics, Tourette's syndrome, or seizures. Use of a MAOI during or within 14 days may result in hypertensive crisis.

Concerta® tablets are non-deformable and do not significantly change shape in the GI tract. Therefore, they should not be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, including esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations.[6]

Mixed amphetamine salts are more potent sympathomimetic amines than methylphenidate. Although both agents are Class II controlled drugs, indicating a significant abuse potential, recent data suggests that oral methylphenidate has a lower potential for abuse.[11] According to evidence-based clinical practice guidelines as well as recent meta-analysis,[2,3,11,12] there is no evidence to suggest that drug abuse results from properly monitored prescribed stimulants.[11,12] The guidelines state that although the abuse of methylphenidate is rare, caution may be indicated in the presence of conduct disorder, preexisting chemical dependency, or a chaotic family. According to the Medical Letter of Drugs and Therapeutics, February 2003, as well as other sources cited, if the risk of drug abuse by the patient or the patient's peers or family is high, a non-stimulant medication may be preferable to methylphenidate or mixed amphetamine salts.[11,12]

Contraindications for Atomoxetine: [5,6,9]
Patients with closed angle glaucoma are not candidates for atomoxetine therapy as this condition is associated with an increased risk for mydriasis. In addition, atomoxetine should not be used in patients taking a monoamine oxidase inhibitor (MAOI), and MAOI treatment should not be initiated within two weeks of atomoxetine discontinuation.[8]

FDA Alerts for Atomoxetine:[10]
Two case reports (via the FDA MedWatch system) of hepatotoxicity in patients taking atomoxetine (one adult, one child) have resulted in the addition of a warning to the product labeling stating: "Post marketing reports indicate that Strattera® can cause severe liver injury in rare cases. Although no evidence of liver injury was detected in clinical trials of about 6000 patients, there have been two reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors, out of more than 2 million patients during the first two years of post marketing experience."

In addition, on September 5, 2005, the FDA directed the manufacturer to revise the labeling for Strattera® to include a boxed warning and additional warning statements regarding an increased risk of suicidal thinking in children and adolescents being treated with this drug. Furthermore, a Medication Guide should be provided directly to patients, their families, and caregivers with information about the risks mentioned above. The Medication Guide is intended to be distributed by the pharmacist with each prescription or refill of this medication.

Misuse and Abuse – Methamphetamine[13]
Reports of misuse and abuse of amphetamines, particularly methamphetamine, have increased in recent years. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased their dosage many times over the recommended dosage. The frequency of abuse of prescriptions for methamphetamine is not known. The resurgence of abuse is likely a result of the relative ease with which methamphetamine can be synthesized illicitly from readily available chemicals such as ephedrine, phenylpropanolamine, or pseudoephedrine. Recent restrictions, including enactment of the US Comprehensive Methamphetamine Control Act of 1996, on the availability of these compounds are intended to reverse this resurgence in misuse and abuse.

According to the U.S. Department of Health and Human Services *Results From the 2002 National Survey on Drug Use and Health: National Findings,* more than 12 million people 12 years and older (5.3%) reported that they had used methamphetamine at least once in their lifetimes.[13] Of those surveyed, 597,000 persons 12 years and older (0.3%) reported use of methamphetamine within the past month. In addition, during the year 1995 the hospitals participating in the Drug Abuse Warning Network (DAWN) reported 15,933 methamphetamine related emergency department (ED) visits. By 1999, the number of methamphetamine related ED visits decreased to 10,447; however, this number rebounded to 17,696 in 2002.

Misuse and Abuse – Methylphenidate[14]
Abuse of oral methylphenidate is rare in comparison to amphetamines. One hypothesis for the limited abuse of methylphenidate is that at orally administered clinical doses, it is a "weak stimulant" and produces slower increases in extracellular dopamine compared to other stimulants. Rapid extracellular dopamine increases are associated with reinforcing effects and increased abuse. However, when methylphenidate is abused, it is usually administered intranasally or intravenously which in turn produces rapid dopamine release. Typically the medication is crushed in order to be administered in these ways. Interestingly, Concerta® can not be crushed and theoretically may offer a decreased potential for abuse. However, it is important to keep in mind that the overall rate of abuse amongst individuals with ADHD is relatively low.

Contraindications for Modafinil [5,6,9]
Patients with hypersensitivity to modafinil or any of its components should not receive modafinil.

IV. Pharmacokinetics

Table 5. Pharmacokinetic Parameters of Cerebral Stimulants and Atomoxetine[5,6,9]

Drug	Protein Binding (%)	Bio-availability	$T_{½}$ (hr)	Onset of Action (min)	Duration of Action (hr)	Metabolism	Excretion
Amphetamine salts (mixed)	20%	Well absorbed	IR 4-6	30-60 minutes	IR 4-6	Extensive liver metabolism	In urine as unchanged drug and inactive metabolites PH dependent; for urine pH < 6.6 the excretion is 67% to 73% of unchanged drug versus pH > 6.7, the excretion is 17% to 43%.
			XR 12	60-90 minutes	XR 10-12 Releases some drug right away, then the rest later (mimics regular BID dosing)		
Dextroamphetamine	Not reported	Well-absorbed	IR 4-6	30-60 minutes	IR 4-6	Extensive liver metabolism	In urine as unchanged drug and inactive metabolites PH dependent; for urine pH < 6.6 the excretion is 67% to 73% of unchanged drug versus pH > 6.7, the excretion is 17% to 43%.
			ER 12	60-90 minutes	ER 6-10 Releases some drug right away, then the rest later (mimics regular BID dosing)		
Methylphenidate	15.2%	10-52%	3-4	IR 30-60 minutes	IR 3-4		

Drug	Protein Binding (%)	Bio-availability	$T_{½}$ (hr)	Onset of Action (min)	Duration of Action (hr)	Metabolism	Excretion
Methylphenidate (continued)	15.2%	10-52 %	3-4	*Metadate ®ER, Ritalin SR* 60-90 minutes	6-8 Releases some drug right away, then the rest later (mimics regular BID dosing)	Liver via de-esterification to an active metabolite	90% in urine as metabolites
				Metadate CD® Ritalin LA® 30-60 minutes	*Metadate CD ®, Ritalin LA®* 8-10 Releases some drug right away, then the rest later (mimics regular BID dosing)		90% in urine as metabolites
				Concerta® 60-120 minutes	*Concerta®* 10 to 14 Releases some drug right away, then the rest later (mimics regular BID dosing)		
Dexmethylphenidate	15%	22-25%	3	30-60 minutes	IR 4-5	Liver via de-esterification to an inactive metabolite	90% in urine as metabolites
					XR 12 Bi-modal plasma concentration-time profile (i.e., two distinct peaks approximately four hours apart)		

Drug	Protein Binding (%)	Bio-availability	$T_{½}$ (hr)	Onset of Action (min)	Duration of Action (hr)	Metabolism	Excretion
Methamphetamine	67%	Extensive	4 to 5	Rapidly absorbed	10-20	Primary site is in the liver At least seven metabolites	62% of dose is eliminated in the urine, 1/3 as intact drug and the rest as metabolites
Modafinil	60%	Rapid absorption	2-4	---	8-12	Extensive liver metabolism (90%)	In urine as 33% unchanged drug and inactive metabolites
Pemoline	50%	Well absorbed	Children 7-8.6 Adult: 12	120 minutes	8-12	Partially by the liver	In urine as unchanged drug (50%); only negligible amounts can be detected in feces
Miscellaneous							
Atomoxetine	98%	63% in extensive metabolizers 94% in poor metabolizers	4	Starts working within a few days to one week, but full effect may not be evident for a month or more	24 hours as long as taken daily as directed	Liver metabolized to active and inactive metabolites	Renal excretion (80%) as inactive metabolite

IR = immediate release; ER, XR = extended-release

V. Drug Interactions

Table 6. Significant Drug Interactions with Cerebral Stimulants and Atomoxetine[15]

Drug	Significance Level	Interaction	Mechanism
Cerebral Stimulants			
Amphetamines (amphetamine salts, dextroamphetamine, methamphetamine)	2	MAO inhibitors: furazolidone	Inhibition of monoamine oxidase by furazolidone
Amphetamines (amphetamine salts, dextroamphetamine, methamphetamine)	1	MAO inhibitors: phenelzine, tranylcypromine	Probably increased norepinephine at synaptic cleft
Amphetamines (amphetamine salts, dextroamphetamine, methamphetamine)	2	Urinary alkalinizers: potassium citrate, sodium acetate, sodium bicarbonate, sodium citrate, sodium lactate, tromethamine	Diminished urinary elimination of unchanged drug
Amphetamines (amphetamine salts, dextroamphetamine, methamphetamine)	2	Guanethidine	May cause decreased guanethidine effectiveness
Amphetamines (amphetamine salts, dextroamphetamine, methamphetamine)	1	Serotonin reuptake inhibitors: fluoxetine, fluvoxamine, paroxetine	Increased sensitivity to sympathomimetic effects and increased risk of serotonin syndrome
Methylphenidates (methylphenidate, dexmethylphenidate)	1	MAO inhibitors: isocarboxaxid, phenelzine, tranylcypromine	May cause hypertensive crisis (headache, hyperpyrexia, hypertension)
Modafinil	2	Triazolam	Induction of GI (major) and hepatic (minor) metabolism (CYP3A4/5) of triazolam by modafinil is suspected
Modafinil	2	Contraceptives, oral	Induction of GI (major) and hepatic (minor) metabolism (CYP3A4/5) of oral contraceptives by modafinil is suspected
Modafinil	2	Ethinyl estradiol	Induction of GI (major) and hepatic (minor) metabolism (CYP3A4/5) of ethinyl estradiol by modafinil is suspected
Miscellaneous			
Atomoxetine	1	MAO inhibitors: isocarboxaxid, phenelzine, tranylcypromine	Possible altered brain monoamine concentrations

VI. Adverse Drug Events

Table 7. Adverse Events Associated with Cerebral Stimulants and Atomoxetine[6,13]

Amphetamine Salts (Mixed) (amphetamine and dextroamphetamine)	
Cardiovascular System	Palpitation (2% to 4%), tachycardia (up to 6% in adults)
Central Nervous System	Insomnia (1% to 27%), headache (up to 26% in adults) Emotional lability (1% to 9%), agitation (up to 8% in adults), dizziness (2% to 7%), nervousness (6%), fever (4%)
Endocrine	Impotence (2% to 4%), libido decreased (2% to 4%)
Gastrointestinal	Appetite decreased (22% to 33%), abdominal pain (14%), dry mouth (up to 33%), nausea (5% to 8%), vomiting (7%), constipation (2% to 4%), anorexia (3%), diarrhea (2% to 6%), dyspepsia (2%), weight loss (1% to 11%)
Genitourinary	
Hepatic	
Hematologic	
Neuromuscular and Skeletal	Twitching (2% to 4%), weakness (2% to 6%)
Respiratory	
Miscellaneous	Photosensitization (2% to 4%)
Methylphenidate and Dexmethylphenidate*	
Cardiovascular System	Angina, cardiac arrhythmia, cerebral arteritis, cerebral occlusion, hyper-/hypotension, palpitation, pulse increase/decrease, tachycardia
Central Nervous System	Depression, dizziness, drowsiness, fever, headache, insomnia, nervousness, neuroleptic malignant syndrome (NMS), Tourette's syndrome, toxic psychosis
Endocrine	Growth retardation
Gastrointestinal	Abdominal pain, anorexia, diarrhea, nausea, vomiting, weight loss
Genitourinary	Necrotizing vasculitis
Hepatic	Liver function tests–abnormal, hepatic coma, transaminases increased
Hematologic	Anemia, leucopenia, thrombocytopenic purpura
Neuromuscular and Skeletal	Arthralgia, dyskinesia
Respiratory	Cough increased, pharyngitis, sinusitis, upper respiratory tract infection
Miscellaneous	Dermatologic: erythema multiforme, exfoliative dermatitis, hair loss, rash, urticaria, accidental injury, hypersensitivity reactions
Methamphetamine*	
Cardiovascular System	Hypertension, tachycardia, palpitation
Central Nervous System	Restlessness, headache, exacerbation of motor and phonic tics and Tourette's syndrome, dizziness, psychosis, dysphoria, overstimulation, euphoria, insomnia
Endocrine	Change in libido
Gastrointestinal	Diarrhea, nausea, vomiting, stomach cramps, constipation, anorexia, weight loss, xerostomia, unpleasant taste
Genitourinary	Impotence
Hepatic	
Hematologic	
Neuromuscular and Skeletal	Tremor
Respiratory	
Miscellaneous	Dermatologic: rash, urticaria Suppression of growth in children, tolerance and withdrawal with prolonged use

* = frequency of adverse events is not defined

Modafinil	
Cardiovascular System	Chest pain (3%), hypertension (3%), palpitation (2%), tachycardia (2%), vasodilation (2%), edema (1%)
Central Nervous System	>10% headache (34%, dose related)
Endocrine	Nervousness (7%), dizziness (5%), depression (2%), anxiety (5%, dose related), insomnia (5%), somnolence (2%), chills (1%), agitation (1%), confusion (1%), emotional lability (1%), vertigo (1%)
Gastrointestinal	Nausea (11%), diarrhea (6%), dyspepsia (5%), xerostomia (4%), anorexia (4%), constipation (2%), flatulence (1%), mouth ulceration (1%), taste perversion (1%)
Genitourinary	Abnormal urine (1%), hematuria (1%), pyuria (1%)
Hepatic	Abnormal LFTs (2%)
Hematologic	Eosinophilia (1%)
Neuromuscular and Skeletal	Back pain (6%), paresthesia (2%), dyskinesia (1%), hyperkinesia (1%), hypertonia (1%), neck rigidity (1%), tremor (1%)
Respiratory	Pharyngitis (4%), rhinitis (7%), lung disorder (2%), asthma (1%), epistaxis (1%)
Miscellaneous	Diaphoresis; Ocular: amblyopia (1%), abnormal vision (1%), eye pain (1%) Postmarketing and/or case reports: agranulocytosis, mania, psychosis
Pemoline*	
Cardiovascular System	
Central Nervous System	Insomnia, dizziness, drowsiness, mental depression, increased irritability, seizure, precipitation of Tourette's syndrome, hallucinations, headache, movement disorders
Endocrine	Suppression of growth in children
Gastrointestinal	Anorexia, weight loss, stomach pain, nausea
Genitourinary	
Hepatic	Increased liver enzyme (usually reversible upon discontinuation), hepatitis, jaundice, hepatic failure (3%)
Hematologic	Aplastic anemia
Neuromuscular and Skeletal	
Respiratory	
Miscellaneous	
Atomoxetine	
Cardiovascular System	Palpitations (4%), systolic blood pressure increased (2% to 9%), orthostatic hypotension (2%), tachycardia (2%)
Central Nervous System	Headache (17% to 27%), insomnia (16%), fatigue/lethargy (7% to 9%), irritability (8%), somnolence (7%), dizziness (6%), mood swings (5%), abnormal dreams (4%), sleep disturbance (4%), pyrexia (3%), rigors (3%), crying (2%)
Endocrine	Dysmenorrhea (7%), libido decreased (6%), menstruation disturbance (3%), orgasm abnormal (2%), weight loss (2%)
Gastrointestinal	Xerostomia (4% to 21%), abdominal pain (20%), vomiting (15%), appetite decreased (10% to 14%), nausea (12%)
Genitourinary	Erectile disturbance (7%), ejaculatory disturbance (5%), prostatitis (3%), impotence (3%); Urinary retention/hesitation (8%)
Hepatic	<1% abdominal pain (right upper quadrant)/ hepatotoxicity, jaundice
Hematologic	
Neuromuscular and Skeletal	Paresthesia (4%), myalgia (3%)
Respiratory	Cough (11%)(4%), sinus headache (3%), sinusitis (6%)
Miscellaneous	Dermatitis (2% to 4%), ear infection (3%), diaphoresis increased (4%), influenza (3%) <1% allergy, angioedema, flu-like syndrome, pruritus, rash, urticaria

* = frequency of adverse events is not defined

VII. Dosing and Administration

Table 8. Dosing and Administration of Cerebral Stimulants and Atomoxetine[5,6,9]

Drug	Strength	Dosage Form	Dosing Frequency
Cerebral Stimulants			
Amphetamine salts (mixed)	IR: 5, 7.5, 10, 12.5, 15, 20, 30 mg	Tablet	**Children** • Not recommended if < 3 years old. **3-5 years** • **Initial** 2.5 mg/day given every morning; increase daily dose in 2.5 mg increments at weekly intervals until optimal response is obtained. • **Maximum dose**: 40 mg/day given in 1-3 divided doses per day. Use intervals of 4-6 hours between additional doses. **Adults and children ≥ 6 years** • **Initial** 5 mg once or twice daily; increase daily dose in 5 mg increments at weekly intervals until optimal response is obtained. • **Maximum dose**: 40 mg/day given in 1-3 divided doses per day. • To avoid insomnia, last daily dose should be administered no less than 6 hours before retiring.
	XR: 5, 10, 15, 20, 25, 30 mg	Capsule	**Adults** • 10-30 mg daily with QD dosing. • May be increased by 5-10 mg per week up to 30 mg per day. **Children ≥ 6 years** • 5-10 mg once daily in the morning; if needed, may increase daily dose in 5-10 mg increments at weekly intervals. • **Maximum dose**: 30 mg/day. • Patients taking the immediate release twice daily form can be switched to an equivalent daily dose of the XR form. • Should be given by noon.
Dextroamphetamine	IR: 5, 10, 15 mg	Tablet	**Children 3-5 years**: • **Initial**: 2.5 mg/day given every morning; increase by 2.5 mg/day in weekly intervals until optimal response is obtained. • **Maximum dose:** 40 mg/day. **Children ≥ 6 years**: • **Initial** 5 mg once or twice daily; increase in increments of 5 mg/day at weekly intervals until optimal response is reached. • **Maximum dose** 40 mg/day.
	ER: 5, 10 mg	Capsule	

Drug	Strength	Dosage Form	Dosing Frequency
Dexmethylphenidate	IR:2.5, 5, 10 mg	Tablet	**Adults and children ≥ 6 years** • **Initial**: 2.5 mg twice daily; dosage may be adjusted in 2.5-5 mg increments at weekly intervals. • **Maximum dose**: 20 mg/day. • Doses should be taken at least 4 hours apart. • When switching from methylphenidate to dexmethylphenidate, the starting dose of dexmethylphenidate should be half that of methylphenidate. • The effectiveness of Focalin XR® for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials.
	ER: 5, 10 mg	Capsule	
Methamphetamine	5 mg	Tablet	**Adults and Children ≥ 6 years** • 2.5-5 mg 1-2 times/day, may increase by 5 mg increments weekly until optimum response is achieved, usually 20-25 mg/day.
Methylphenidate	IR: 5, 10, 20 mg	Tablet	**Age ≥ 6 years** • Initial: 0.3 mg/kg/dose or 2.5-5 mg/dose given before breakfast and lunch; increase by 0.1. mg/kg/dose or by 5-10 mg/day at weekly intervals; usual dose: 0.5-1 mg/kg/day. • **Maximum dose**: 2 mg/kg/day or 60 mg/day. Note: Discontinue periodically to re-evaluate or if no improvement occurs within 1 month.
	ER: 10, 20, 30, 40 mg	Capsule	**Age ≥ 6 years** • **Initial:** 20 mg once daily; may be adjusted in 10-20 mg increments at weekly intervals. • **Maximum dose**: 60 mg/day. **Ritalin LA** • Dose conversions from immediate-release or other extended-release products are included in the package insert.
	ER: 10, 20 mg	Tablet	
	ER: 18, 27, 36, 54 mg	Tablet	• **Initial**: 18 mg once daily in the morning. • Dosage may be adjusted weekly in 18 mg increments. • **Maximum dose**: 54 mg per day. • Patients converting from immediate-release or sustained-release methylphenidate may follow the dosage conversion chart included in the official labeling. • Dosing should be completed by noon.

Drug	Strength	Dosage Form	Dosing Frequency
Modafinil	100, 200 mg	Tablet	**Adults** • Narcolepsy, OSA: Initial: 200 mg as a single daily dose in the morning. • SWSD: Oral: Initial: 200 mg as a single dose taken ~1 hour prior to start of work shift. **Pediatrics** • Not approved for use in children. Note: Doses of 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit.
Pemoline	18.75, 37.5, 75 mg	Tablet	**Age ≥ 6 years** • **Initial** 37.5 mg/day • May increase by 18.75 mg at weekly interval to usual effective dose of 56.25-75 mg/day. • **Maximum Dose**: 112.5 mg/day.
Miscellaneous			
Atomoxetine	10, 18, 25, 40, 60 mg	Capsule	**Adults**: • **Initial**: Begin with 40 mg daily. • Increase after > 3 days to target dose of 80 mg. • **Maximum dose**: 100 mg daily. **Children:** • < = 70 kg, start with 0.5 mg/kg per day. • Increase after > 3 days to target dose of 1.2. mg/kg /day divided QD-BID. • Max dose: 100 mg daily or 1.4 mg/kg. • If > 70 kg, use adult dose. • Not studied in children < 6 years old. • May be discontinued without taper. • Allow several weeks for maximal response.

Table 9. Special Dosing Considerations[5,9]

Drug	Renal Impairment	Hepatic Impairment	Pregnancy Category	Comments
Amphetamine salts (Mixed)	Renal elimination is dependent on urinary PH. Excretion is increased in acidic urine and decreased in alkaline urine.		C	
Dexmethylphenidate				
Methamphetamine				Associated with high rate of dependence and abuse
Methylphenidate				
Modafinil	Inadequate data to determine safety and efficacy in severe renal impairment.	Dose should be reduced to one-half of that recommended for patients with normal liver function.	C	High incidence of off-label use
Pemoline	Cl <50 mL/minute: Avoid use		B	May cause rare but severe hepatotoxicity
Miscellaneous				
Atomoxetine		Moderate hepatic insufficiency (Child-Pugh class B): All doses should be reduced to 50% of normal. Severe hepatic insufficiency (Child-Pugh class C): All doses should be reduced to 25% of normal.	C	Maximal response typically occurs after 4 weeks of treatment Metabolized by CYP2D6, poor metabolizers (7% Caucasians, 2% African Americans) may have a 5 fold increase in C_{max} and 10 fold increase in AUC

VIII. Effectiveness

Table 10. Efficacy of Cerebral Stimulants and Atomoxetine in ADHD[16-28]

Reference	Study Design	N	Treatment Regimen	Primary Outcome(s)	Results
Mixed Amphetamine Salts- IR versus Methylphenidate IR					
Pliszka[16]	Randomized, double-blind, placebo-controlled, parallel	58	• AMP* IR 12.5 mg +/- 4 mg daily • MPH† IR 25 +/-13 mg daily • Placebo Duration: 3 weeks	CGI (parent and teacher)	• More responders on both CGI scores with AMP versus MPH or placebo. ($p < 0.05$) • Behavioral effects of AMP appeared to persist longer than with MPH. • Questionable equipotent dosing algorithm. (70% of children on AMP received once daily dosing versus only 15% of those on MPH).
Faraone[17]	Meta-analysis 8 studies	--	• AMP-IR • MPH-IR • various doses for both Duration: 3 weeks up to 8 weeks	CGI (parent, teacher and investigator)	• Combined results showed slightly greater efficacy with AMP versus MPH in clinician and parents ratings. ($p < 0.05$) • No difference in CGI scores with teacher ratings.
Pelham[18]	Randomized, double-blind, placebo-controlled, crossover	N=25	• MPH-IR 10 or 17.5 mg BID • AMP-IR 7.5 or 12.5 mg BID • Placebo • Agents were given in random order with conditions changing daily for 24 days Duration: 6 weeks	CTRS-R and CPRS-S	• The doses of AMP that were assessed produced greater improvement than did the assessed doses of MPH, particularly the lower dose of MPH. ($p < 0.01$). • AMP was generally more efficacious in reducing negative behaviors and improving academic productivity than low dose MPH (10 mg BID) throughout the course on the entire day. The differences were more pronounced when the effects of MPH were wearing off at midday and late afternoon/early evening. ($p <0.025$) • Conversely, AMP 7.5 mg BID and MTH 17.5 mg BID produced equivalent behavioral changes throughout the entire day.($p <0.05$) • Both drugs produced low and comparable levels of clinically significant side effects. • Clinical recommendations made by both open and

Reference	Study Design	N	Treatment Regimen	Primary Outcome(s)	Results
					blinded clinical staff at the end of the assessment were more likely to favor AMP than MTH.
Mixed Amphetamine- IR versus Adderall XR®					
McCracken[19]	Randomized, double-blind, placebo-controlled, crossover	51	• AMP- IR 10 mg QD • Adderall XR® 10, 20, or 30mg QD • Placebo Duration: 5 weeks	SKAMP **Secondary:** parent global assessment	• AMP and Adderall XR® have similar efficacy, and both are better than placebo ($p < 0.0001$) with attention and deportment.
Adderall XR® versus Placebo					
Biederman[20]	Randomized, double-blind, placebo-controlled	584	• Adderall XR® 10,20, or 30 mg QD • Placebo Duration: 3 weeks	CGI (teachers and parents)	• Adderall XR® had greater efficacy than placebo. • CGI: teachers – 10 mg group = -5.3, 20 mg group = -6.0, 30 mg group = - 6.4, and placebo = - 0.9. ($p < 0.001$)
Methylphenidate versus Dextroamphetamine					
Efron [21]	Randomized, double-blind, crossover	125	• MPH IR (0.3 mg/kg/dose) BID • DEX‡ (0.15 mg/kg/dose) BID • Received drug for 2 weeks the then crossed over to receive the other stimulant for 2 weeks Duration: 4 weeks	CTRS-R	• Degree of response as measured by the CTRS-R was greater for MPH than for DEX. ($p < 0.001$) • Mean improvement on the hyperactivity index was 2.6 points greater with MPH than with DEX. ($p < 0.001$) • MPH was the preferred drug for 46% of parents compared to 37% for DEX.
Methylphenidate IR versus Methylphenidate ER					
Wolraich[22]	Randomized, double-blind, placebo-controlled, parallel	282	• Concerta® 18-54 mg QD • MPH IR 5-15 mg TID • Placebo Duration: 28 days	CTRS-R **Secondary:** CGI (teachers and parents)	• CTRS-R teachers scores at the end of week 1 showed statistically significant improvement with both Concerta® (mean: 5.58 ± 3.64) and MPH IR TID (mean: 5.70 ± 3.84) versus placebo (9.87 ± 4.09). ($p < 0.001$) • Similar CTRS-R results were seen at study endpoint for both active treatment groups. • CTRS-R differences between Concerta® and MPH

Reference	Study Design	N	Treatment Regimen	Primary Outcome(s)	Results
					were not statistically significant. • CGI – teachers rated good or excellent efficacy for 42 % of Concerta® group, 46% of MPH group, and 17% placebo. • CGI- parent scores were similar. .
Pelham[23]	Randomized, double-blind, placebo-controlled, crossover	68	• Concerta® 18-54 mg QD • MPH IR 5-15 mg TID • Placebo Duration: 1 week	CGI (teacher and parents)	• Concerta® and MPH demonstrated similar efficacy but were both better than placebo. ($p < 0.05$) • Concerta® was significantly better than MPH on 2 parent rating scores , and when asked, more parents preferred Concerta® over MPH or placebo.
Comparative Methylphenidate ER Trials					
Lopez[24]	Randomized, double-blind, placebo-controlled, crossover	36	• Ritalin LA® 20 mg QD • Concerta®18 mg or 36 mg QD • Placebo Duration: 28 days	SKAMP Scale	• Differing PK profiles translate into differing effects on attention and deportment.
Swanson[25]	Randomized, double-blind, placebo-controlled, crossover	---	• Concerta® 18-54 mg QD • Metadate CD® 20-60 mg QD • Placebo Duration: 7 weeks	SKAMP	• Concerta® and Metadate CD® demonstrated similar efficacy, and both are better than placebo. • Efficacy was related to Cpmax, Metadate CD® > Concerta® in the morning; both agents were equivalent in the afternoon; and Concerta® was more efficacious in the early evening.
Wilens[26]	Prospective, observational study	407	• Long-term (Concerta)® 18-54 mg QD Duration: 1 year	1 year tolerability	• Compared to baseline, Concerta® was associated with minor clinical, although statistically significant, blood pressure elevations (DBP) 3.3 mm Hg, $p < 0.001$) and HR (3.9 bpm, $p < 0.0001$) at 12-month end point.

Reference	Study Design	N	Treatment Regimen	Primary Outcome(s)	Results
Additional Cerebral Stimulant Trials					
Grenhill[27]	Randomized, double-blind, placebo-controlled, parallel	321	• Metadate CD® (20-60 mg) QD • Placebo Duration: 3 weeks	CGI -teacher **Secondary:** CGI - parents	• Metadate was more efficacious versus placebo. • CGI–teacher: decreased from 12.7 to 4.9 with • Metadate CD® versus 10.5 to 10.3 with placebo. • CGI–parents: decreased from 13.6 to 7.4 with Metadate CD® versus placebo (decreased from 12.9 to 10.1. ($p < 0.001$ for both scales)
Pelham[28]	Randomized, double-blind, placebo-controlled, crossover	22	• MPH IR • MPH ER • DEX ER • Pemoline	Evaluated social behavior during activities, classroom performance, and performance on a continuous performance task	• Generally equivalent and beneficial effects seen with all four medications. • DEX ER and pemoline tended to produce the most consistent effects. • The continuous performance task results showed that all four medications had an effect within 2 hours, and the effects lasted for 9 hours.
Atomoxetine versus Placebo					
Kratochvil, 2002[29]	Open label, head-to-head trial	228	• Atomoxetine titrated up to 2 mg/kg/day (184) • MPH up to 60 mg (44) daily Duration: 10 weeks	CGI -S ADHD-RS **Secondary:** CPRS-RS	• Both drugs were associated with marked improvement in inattentive and hyperactive-impulsive symptom clusters. • No statistically significant differences between treatment groups on all of the outcome measures. • Safety and tolerability were also similar between the two drugs and both medications were well tolerated.
Biederman, 2002[30]	Pooled subgroup analysis from 2 double-blind, placebo-controlled trials	51 females	• Atomoxetine 1.2-1.8 mg/kg/day • Placebo Duration: 9 weeks	CGI- S ADHD-RS **Secondary:** CPRS-RS	• Statistically significant differences seen weeks 3 to 8 in all scales versus placebo. ($p < 0.0002$)

Reference	Study Design	N	Treatment Regimen	Primary Outcome(s)	Results
Michaelson, 2001[31]	Randomized, open-label, placebo-controlled	297	• Atomoxetine 1.2-1.8 mg/kg/day • Placebo Duration: 8 weeks	CPRS-RS ADHD-RS	• Atomoxetine 1.2 mg/kg showed significant decreases in all scales of CPRS-RS. ($p < 0.05$) • Significant reduction in ADHD-RS with both active groups. ($p < 0.05$) • No difference between 1.2 and 1.8 mg/kg/day treatment arms.
Spencer, 2002[32]	Randomized, double-blind, placebo-controlled (pooled data from 2 trials)	291	• Atomoxetine up to 90 mg daily • Placebo Study # 2 included MTH titrated up to 60 mg BID Duration: 9 weeks	CGI- S ADHD-RS **Secondary:** CPRS-RS	• Significant mean reductions in both active groups in all scales (both studies) ADHD-RS ($p < 0.001$), CPRS-RS. ($p = 0.023$ for study #1 and $p < 0.001$ for study #2) • Comparable efficacy between the atomoxetine and MPH treatment groups.

AMP = Mixed amphetamine salts; MPH = methylphenidate; DEX = dextroamphetamine
DBP = Diastolic blood pressure

Assessment Scales: ADHD-RS – correlates to DSM-IV symptoms; CGI = Clinical Global Impression (assesses impairment from symptoms); CGI-S = Clinical Global Impression of Severity ;CPRS-R = Connors Parent Rating Scale- Revised; CTRS-R = Connors Teacher Rating Scale-Revised; CPRS-RS = Connors Parent Rating Scale: Short Form; SKAMP= assesses classroom manifestations of ADHD

Table 12. Efficacy of Modafinil in Narcolepsy[33-38]

Reference	Study Design	N	Treatment Regimen	Primary Outcome(s)	Results
U.S. Group[33]	Randomized, double-blind, placebo-controlled trial	271	• Modafinil 200 mg or 400 mg QD • Placebo • Duration: 9 weeks	MWT, CGI-C **Secondary:** MSLT, ESS	• Modafinil was effective for treatment of daytime sleepiness in narcolepsy with up to 9 weeks of daily use. • MWT: improved for both modafinil groups versus placebo ($p < 0.001$) at every follow-up visit. (weeks 3,6,9) • MSLT: 5.1 minute increase with modafinil 400 mg versus placebo ($p < 0.001$) impact of 200 mg modafinil dose was not significant. • ESS: reduced for both treatment groups ($p < 0.001$) versus placebo • CGI-C: improved for both treatment groups ($p < 0.03$) Percent Improvement ($p < 0.03$): Modafinil 200 mg = 58% Modafinil 400 mg = 61 % Placebo = 38 %
U.S. Group[34]	Randomized, unblinded, controlled trial, parallel	447	• Modafinil 200 mg or 400 mg QD • Placebo • Duration: 9 weeks • (extension phase of Study#1)	MSLT, MWT CGI-C **Secondary:** ESS	• Modafinil 200 mg and 400 mg were more effective for control of excessive daytime sleepiness compared to placebo. Modafinil reduced all measures of sleepiness. ($p < 0.05$)
Broughton[35]	Randomized, placebo-controlled trial, crossover	75	• Modafinil 100 mg or 200 mg QD • Placebo • Duration: 6 weeks	MWT **Secondary:** ESS	• Modafinil was effective for keeping narcolepsy patients awake. ($p < 0.05$) • MWT: increased by 40% with modafinil 200 mg ($p < 0.002$) and 54% with 400 mg dose. ($p< 0.001$) • ESS: decreased the likelihood of falling asleep with both treatment groups versus placebo. Modafinil 200 mg ($p < 0.018$) and modafinil 400 mg. ($p < 0.0009$)

Reference	Study Design	N	Treatment Regimen	Primary Outcome(s)	Results
Billard[36]	Randomized, crossover trial,	50	• Modafinil 300 mg (in divided doses) or 100 mg AM and 200 mg at noon or vice versa • Placebo • Duration: 12 weeks	MWT, CGI-C **secondary**: sleep logs	• MWT: Modafinil improves daytime alertness ($p < 0.05$) • Sleep logs showed a reduction in daytime sleepiness.
Boivin[37]	Randomized, controlled trial, crossover	10	• Modafinil 100 mg or 200 mg QD • Placebo • Duration: 8 weeks	PSG, before and after, FCRTT	• Modafinil improved subjective alertness, and improved performances on FCRTT questionnaires with no harmful effects on nocturnal sleep. ($p< 0.05$)
Schwartz[38]	Randomized, open label safety study	40	• Modafinil 200 mg then 400 mg in patients who stopped MPH abruptly with or without a 2 day washout period • Duration: 5 weeks	ESS	• Switching from MHP to modafinil was well tolerated with or without a 2 day washout period. • Mean Epworth Sleep Scores were <12 for each group. ($P < 0.05$)

MPH = methylphenidate

Assessment Scales:
CGI-C = Clinical Global Impression of Change; ESS = Epworth Sleep scale; FCRTT = Four Choice Reaction Time Test: MSLT = Multiple Sleep Latency Scale; MWT = Maintenance of Wakefulness Test, PSG = Polysonogram

Additional Evidence

Dose Simplification:
Once daily formulations increase patient compliance, and eliminate the need for medication dosing in schools. Prescribing immediate release stimulants that require dosing during school is problematic, especially with controlled drugs which have an abuse potential. Extended-release formulations eliminate the need for additional doses during the school day. A few studies compared immediate-release stimulants with extended-release, once daily products. A study by Lage, et al[39] looked at a claims database of patients who took methylphenidate immediate-release (IR) TID versus methylphenidate extended-release (XR, Concerta®) QD. They found that the XR patients had better compliance, were less likely to switch and were less likely to discontinue the medication (all statistically significant). XR usage was also associated with significantly fewer emergency room visits and fewer general practitioner visits. Another study looked at patient satisfaction and health related quality of life after switching from methylphenidate IR or methylphenidate XR (Concerta®) to mixed amphetamine salts XR (Adderall XR®). They found that quality of life was statistically improved in the mixed amphetamine salts XR group along with increases in physician and parent satisfaction.[40]

Stable Therapy:
Cerebral stimulants should not be discontinued abruptly as this may potentiate ADHD symptoms. However, atomoxetine may be discontinued without tapering.[5]

Impact on Physician Visits:
A search of Medline and Ovid did not reveal data pertinent to medical or physician resource utilization. However, it should be mentioned that cerebral stimulant medications for ADHD may be prescribed for a maximum of 30 days per prescription whereas atomoxetine may have up to 11 refills per prescription. The availability of prescription refills may in turn decrease the frequency of physician visits.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this AHFS drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current AL Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the AL Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the AL Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0 - $25 per Rx
$$	$26 -$50 per Rx
$$$	$51-$75 per Rx
$$$$	$76-$100 per Rx
$$$$$	$101-$150 per Rx

Rx = prescription

Table 9. Relative Cost of Cerebral Stimulants (ADD/ADHD Agents) and Atomoxetine

Generic Name	Form	Example Brand Name(s)	Brand Cost	Generic Cost
Amphetamine salts (mixed) (amphetamine/dextroamphetamine)	Extended-release capsule, tablet	Adderall®*, Adderall XR®	$$$-$$$$	$$
Dextroamphetamine	Extended-release capsule, tablet	Dexedrine®*, Dextrostat®*, Dexedrine Spansule®	$$$	$$
Dexmethylphenidate	Extended-release capsule, tablet	Focalin®, Focalin XR®	$$-$$$$	N/A
Methamphetamine	Tablet	Desoxyn®	$$$$$	N/A
Methylphenidate	Chew tablet, extended-release capsule, extended-release tablet, solution, tablet	Concerta®, Metadate CD®, Metadate ER®*, Methylin®*, Methylin ER®*, Ritalin®*, Ritalin LA®, Ritalin SR®*	$$-$$$	$-$$
Modafinil	Tablet	Provigil®	$$$$$	N/A
Pemoline	Tablet	Cylert®*	$$$	$$
Miscellaneous				
Atomoxetine	Capsule	Strattera®	$$$$	N/A

* Generic is available in at least one dosage form or strength.
N/A = not available

X. Conclusions

Amphetamines and methylphenidate have demonstrated efficacy for lowering ADHD symptom scores versus placebo. There are a few clinical trials that demonstrate a slight statistically significant advantage with amphetamines versus methylphenidate.[16-18] However, these studies were small and of short duration and the overall body of evidence clearly indicates no differences in efficacy.[2] Studies cited in the AAP Clinical Practice Guidelines also did not detect an efficacy difference between amphetamines and methylphenidate when dosed equipotently.[2] As a result, the selection of a particular stimulant medication is not based on differences in efficacy.

There are several generic formulations of the short-and intermediate-acting cerebral stimulants. All brand short- and intermediate-acting cerebral stimulants within the class reviewed are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

Even though there are pharmacokinetic differences between the extended-release long-acting cerebral stimulants, no differences in efficacy have been reported.[24,25,28] The advantage of the once daily dosage forms is the avoidance of dosing medication during school hours, since both methylphenidate and mixed amphetamine salts are class II controlled substances, and drug diversion as well as school policies and procedures remain paramount issues. Administration of medications during school hours, especially C-II medications, is difficult since the medication must be administered by a school nurse. In addition, HIPAA mandates patient confidentiality, and ADHD treatment requires added security. Therapeutic effects with cerebral stimulants are dose-dependent, and the need to control the hyperactivity and inattention components during school hours is principally for continued academic and social success, therefore long-acting formulations taken with breakfast may have a pharmacokinetic advantage that may or may not translate into a therapeutic advantage.[23, 25, 39, 40]

There are no long-acting cerebral stimulants that are available generically. The clinical data reports that the immediate-release and extended-release products possess comparable safety and efficacy. Methylphenidate has been the most extensively studied and prescribed cerebral stimulant for ADHD and data suggests that it may possess a lesser degree of abuse potential.[2,11] But addiction to methylphenidate can and does occur. However; little is known about the actual prevalence of methylphenidate abuse. Research shows that people with ADHD rarely become addicted to stimulant medications when taken in the form and dosage prescribed.[41] The majority of stimulant abuse tends to occur when used for non medical purposes and with the immediate release products.[41] Therefore the long-acting cerebral stimulants reviewed in this class offer significant clinical advantage in general use over the other brands, generics, and OTC products in the same class, but are comparable to each other.

Based upon a lack of evidence to support the safety of atomoxetine long term, and the limited evidence to support efficacy, the brand version of atomoxetine offers no significant clinical advantage over other alternatives in general use. It may be appropriate for some patients, however, such as patients that are refractory to stimulants. Other clinical scenarios where atomoxetine may be appropriate include: instances of substance abuse history, unacceptable side effects, or significant comorbid conditions. [5,6,9] Although atomoxetine has demonstrated efficacy in reduction of ADHD symptoms compared to placebo, there is limited comparative data versus methylphenidate or amphetamines at this time.[29-32] In addition, there is currently insufficient data to determine the role of atomoxetine in ADHD therapy.

There is limited data at this time to establish the role of modafinil the treatment of narcolepsy. Amphetamines and methylphenidate are the mainstay of treatment for narcolepsy based on a long record of clinical experience.[7] In addition, there are no head to head trials comparing modafinil to conventional therapies at this time.

XI. Recommendations

No brand of short- or intermediate-acting cerebral stimulant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand long-acting cerebral stimulant is selected as a preferred agent.

No brand of atomoxetine is recommended for preferred status, regardless of cost.

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